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THE THERAPEUTIC USE OF DIGITALIS

BY

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PREFACE

In reviewing the extensive literature on the drugs of the digitalis group, the writer has endeavored to keep constantly in mind the needs of the physician who is faced with the problems of the treatment of heart disease. Special emphasis has been placed therefore on recent clinical studies, and reference to much of the work of the older pharmacologists, no longer of practical significance, has been omitted. The monograph deals largely with the action of digitalis and its allies on man, especially in its relation to specific types of heart disease. An endeavor has been made to correlate the action of these drugs with the newer knowledge of the pathological physiology of the heart.

An attempt has been made to present such facts regarding the more useful members of the digitalis group that may give the physician using them some idea of their history, properties, source, composition and relative potency. It has also seemed desirable to discuss some phases of the subject with the hope of correcting certain fallacies that appear to have a strong hold on the medical practice of our time.

The method of treating the subject of the therapeutic use of digitalis is indicated by the table of contents. Each section and subsection has been written with the idea that it may be read without regard to other portions of the monograph. On account of the detailed table of contents it has seemed unnecessary to prepare an index.

The more obvious gaps in the present day knowledge of digitalis and its allies have been pointed out. It is hoped that this monograph may serve to stimulate further study of digitalis not only by laboratory workers, but especially by physicians at the bedside, in hospital and private practice, where so much of value has recently been gained, and where so much remains to be learned.

G. Canby Robinson.

January 1, 1923

THE THERAPEUTIC USE OF DIGITALIS

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I. INTRODUCTION

Digitalis was introduced into medicine by William Withering (163), who published at Birmingham, England, in 1785, his book entitled "An account of the foxglove and of its medicinal uses, with practical remarks on dropsy and other diseases." This book deserves a place among the medical classics, not only because it introduced digitalis into medicine, but also because it reveals an attitude of mind which should serve as a model for all who wish to bring forward any new therapeutic agent.

The words of Withering form a fitting introduction to this review. He says:

It is much easier to write upon a disease than upon a remedy. The former is in the hands of nature, and a faithful observer, with an eye of

tolerable judgment, cannot fail to delineate a likeness. The latter will ever be subject to the whims, the inaccuracies and the blindness of mankind.

Withering's views on pharmacology did not differ widely from those of today, as is indicated by the opening paragraphs of his account of foxglove.

As the more obvious and sensible properties of plants, such as color, taste and smell have but little connexion with the diseases they are adapted to cure, so their peculiar qualities have no certain dependence upon their external configuration. Their chemical examination by fire, after an immense waste of time and labour, having been found useless, is now abandoned by general assent. Possibly other modes of analysis will be found out, which may turn to better account, but we have hitherto made only a very small progress in the chemistry of animal and vegetable substances. Their virtues must therefore be learnt, either from observing the effects upon insects and quadrupeds; from analogy, deduced from already known powers of some of their congenera, or from the empirical usages and experience of the populace.

The first method has not been much attended to, and the second can only be perfected in proportion as we approach toward the discovery of a truly natural system; but the last, as far as it extends, lies within the reach of every one who is open to information, regardless of the source from whence it springs.

It was a circumstance of this kind which first fixed my attention on foxglove.

Withering indicates, at the outset, some of the various phases of study through which digitalis was destined to go. First, the empirical studies which have almost invariably marked the beginning of progress in therapeutics. Second, the study of the effects of the drug in lower animals, the period of experimental pharmacology. Third, the study of the effects of the drug on man by exact methods which allow observations approaching in accuracy those made on lower animals, the recent, present-day period. The relation of chemical structure to pharmacological action, although "abandoned by general assent" in Withering's day, represents the pharmacology of the future, which is today beginning to show far-reaching possibilities.

As far as digitalis is concerned, however, scarcely a beginning has been made.

The literature on digitalis and its allies is very extensive, and an attempt to cover it completely has not been made. This review will include the more recent work dealing especially with the action of the drug on man, and particularly on patients suffering from heart and circulatory diseases. The literature of experimental pharmacology will be reviewed only in so far as is necessary to lead up to and explain the effects of digitalis as observed in therapeutics. There remain certain points which are better known on animals and the direct application of experimental results is necessarily made, in some instances, in the therapeutic use of digitalis. The direct application has certain difficulties which will be pointed out, and as the methods for studying the effects of the drug on patients become more and more exact, the application of experimental facts becomes less and less necessary. The relation of experimental pharmacology to the therapeutic use of digitalis will be discussed subsequently.

II. HISTORICAL DATA

Foxglove was first "noticed" according to Withering (163) by Fuchsius in 1542, who gave it the botanical name Digitalis purpurea because of the resemblance of its flowers to a finger or a thimble ("finger-hut") and because of its purple color. Fuchsius also mentioned the emetic action of the plant when eaten. Boerhaave considered foxglove a poison but Alston held that it was one of the native plants of England which should be considered a medicine of great virtue. Haller mentioned foxglove as a purge. Withering also relates the observations of Salerne, who made apparently the first experiments with the plant on animals in 1748. He fed the leaves to turkeys and described both the fatal and non-fatal effects which he observed. The emetic and purgative effects of foxglove were known before Withering's time, and the plant had been used in ointments and also as an expectorant.

Withering undertook the use of foxglove because he was informed of a secret remedy by which an old woman of Shropshire was often able to relieve and cure patients with dropsy to whom no help could be given by some of the leading medical men of the day. He obtained

the formula which she used, consisting of some twenty herbs, and from his knowledge of medicinal plants, concluded that foxglove was the one whose action was beneficial. Withering's book was written after an experience with the drug covering a period of ten years. He gives an account of one hundred and sixty-three patients to whom he had given the drug, and also published communications from other physicians whom he had told of his early results. He states that in order to prevent any unwarranted enthusiasm for the drug, he has reported all patients to whom the drug was given without selection, and warns his readers from being led astray by the communications of other physicians from whom he had received reports of selected cases. The case reports are concise, clear and graphic but, strange to say, deal exclusively with the diuretic effects of the drug and the disappearance of dropsy. Withering observes the fact that digitalis slowed the pulse, especially when given in large doses, but he did not associate this effect with the benefit of patients suffering from heart disease. In fact it is evident that he considered the diminution of the heart rate as a sign that the maximum dose of the drug had been given, for he says: "Let the medicine be continued until it either acts on the kidneys, the stomach, the pulse or the bowels; let it be stopped upon the first appearance of any one of these effects." This is sound advice, which for many years, has been disregarded.

The appearance of Withering's book one hundred and thirty-seven years ago represents the beginning of the period of study of digitalis by direct observations on patients, the drug being given for purely empirical reasons. The manner or method of its action were unknown and there were but few established facts on which to base hypotheses.

Cushny, Morris and Silverberg (32) have given a brief review of the varying opinions regarding digitalis following the publication by Withering. In 1799 Ferriar published "An essay on the medical properties of Digitalis purpurea or foxglove" in which he said that "the power of reducing the pulse is the true characteristic" of the drug, diuresis being a less constant and a less essential quality of the plant.

Beddoes in 1801 stated that "in a certain dose, digitalis will increase the activity of the arterial system." In this same year, Kinglake also showed that the force of the pulse was increased by the drug; and in

1839, according to Cushny, Blake discovered that digitalis caused an elevation of blood pressure. In spite of these observations, digitalis was generally considered a cardiac sedative. Its use was advised by Pereira in 1840 in cases of pulmonary hemorrhage and aneurism. This idea was supported by Traube, who discovered that digitalis stimulated the vagus nerves during his pioneer experiments on animals in 1851, but it was abandoned after Schmiedeberg's (138) classical work published in 1874, which showed the effect of digitalis on the frog's heart. A comprehensive view of the history of the pharmacology of digitalis up to 1883 is given by Schmiedeberg (139) and will not be taken up here.

In spite of the masterly presentation of Withering, digitalis did not gain a firm foothold in medical practice until recent years. Pratt (122) has reviewed the various treatises on heart disease written by eminent English authors, in order to find out the dependence that was placed in the drug. Beginning with Allan Burns, who in 1809, published the first general treatise on heart disease, and going through Hope, Stokes, Latham and Walshe, as well as our own Austin Flint, he found that they paid little or no attention to Withering's teaching and never discovered for themselves the great value of digitalis in cardiac failure. Pratt is unable to say who deserves the credit for impressing upon the medical world the value of Withering's work. He says, however, that "Sir James Mackenzie, working over a hundred years later, was the first clinician to demonstrate conclusively the correctness of Withering's instructions regarding the administration of digitalis."

III. THE DIGITALIS GROUP

There are a number of drugs which resemble digitalis more or less closely from the point of view of their pharmacological action, which are usually included in the so-called digitalis group. They act upon the heart muscle and the musculature of arteries and stimulate certain nervous structures including the vagus centre. In this group are to be included digitalis, strophanthus, squill, apocynum, convallaria, adonis, hellebore and oleander. Abel and Macht (1) have isolated a digitalis-like body from the poison of the tropical toad, Bufo agua. They call this substance bufagin. Its marked action on the heart,

its vaso-constrictor action and its powerfully stimulating action on the vagus centre led them to class this drug with the most effective members of the digitalis series. Many substances, of which barium may serve as an example, have a superficial resemblance in their action to digitalis, but should not be considered as members of the group. The characteristic digitalis effects are produced in experimental animals by all the drugs that belong properly in the group, the difference between them being quantitative. For this reason the various members of the group have been used more or less interchangeably in experimental work. In their use in clinical medicine, differences have been discovered, especially in dosage, rapidity and duration of action and absorption from the gastro-intestinal tract which makes their differentiation important.

As digitalis and strophanthus are by far the most important drugs of the group from the therapeutic standpoint, this review will deal with them almost exclusively.

1. Digitalis

The drug is usually derived from the leaves of Digitalis purpurea. The leaves are gathered and dried and then the drug is prepared for use by powdering the leaves or by extracting their active principles by water, alcohol or other solvents. Digitalis and its active principles have been prepared in many forms for therapeutic purposes and the best known of the preparations will be discussed when the question of the administration of the drug to man is considered.

The active principles contained in Digitalis purpurea were first studied by Schmiedeberg (138). He found that from fresh digitalis leaves, at least three active glucosides could be obtained which he called digitoxin, digitalin and digitalein. Digitoxin is the most highly active of these substances, and produces all the characteristic pharmacological effects. It is practically insoluble in water, but is easily soluble in alcohol. Roth (136) has recently given a brief review of the chemical investigations of the digitalis bodies. He says that Kiliani, who has made the most important chemical study of digitalis, gives $C_{34}H_{54}O_{11}$ as the formula for digitoxin, while the true or crystallized digitalin has the formula $C_{35}H_{56}O_{14}$. Digitalin is easily

soluble in alcohol and very slightly soluble in water. It is found in larger quantities in the seeds than in the leaves of digitalis.

The term "digitalin" has been used to denote a variety of preparations which has served to bring into the literature considerable confusion. Hatcher and Eggleston (78) state that the name is meaningless without a qualifying term, and it has been used to mean digitoxin, true digitalin, or a mixture of the latter with digitonin, a saponin-like substance. Other instances of such confusion are found in the literature dealing with the digitalis group. This is much to be regretted and careful consideration should be given to this question of terms. A general agreement in this connection is much desired.

Digitalein is a water-soluble glucoside which Schmiedeberg considered a pure substance, while Kiliani looked upon it as a mixture.

Besides the active substances that have been mentioned, digitalis also contains a saponin-like body called digitonin. It is inert as regards the characteristic digitalis effects, but according to Roth (136), it is due to the digitonin that aqueous solutions of digitalis leaves contain the water-insoluble substances, digitalin and digitoxin.

As stated by Roth, Kraft in 1912 isolated from a watery extract a glucoside which he named "gitalin" which he considered a purified digitalein. Both Kiliani and Rosenthaler worked with gitalin in 1914, and concluded independently that it was not a definite substance and could be resolved into constituents having unlike chemical and pharmacological properties. Several other investigators have attempted to shed further light on the chemical constituents of digitalis and in 1913 Kolipinski isolated an acid resin which he named "digitalic acid." He concluded from his many animal experiments that "digitalic acid" possessed all the virtues, without any of the poisonous properties of digitalis when used in therapeutic or larger doses. He also considered that it produced no cumulative effects and was not irritating when used subcutaneously. The work of Kolipinski would have held promises of definite advance in the therapeutic use of digitalis, if it had been confirmed by further study, but the investigations of Sharp and of Smith in 1914, failed to substantiate Kolipinski's claims, as both reached the conclusion that digitalic acid has no pharmacological effects whatever, being an inert substance.

2. Sources of digitalis

For many years, the English-grown leaf, especially those marketed by Allan, was considered the standard source. During recent years, however, the greater part of the supply of digitalis used in the United States came, according to Roth (135), from Germany and Austria. When this source of supply was cut off during the years following 1914, by the turmoil of war, attention in the United States was turned to the home-grown product. Wilbert pointed out that Digitalis purpurea grew abundantly in California, Oregon and Washington and, to some extent, in West Virginia. In these states, it is found growing wild, and is considered a "weed" in various parts of the country. American leaves were used by Rowntree and Macht (137) in 1916, who prepared infusions from them as well as from European leaves, and when the pharmacological activity of these infusions was determined on cats they found that the highest potency was possessed by the infusions of American leaves.

Roth (135) investigated the activity of wild American digitalis in 1917 using leaves gathered in the States of Oregon and Washington. The leaves were air-dried and tinctures were made of them, the assays being conducted by the one-hour frog method. He found that the wild digitalis from the Northwestern States was of sufficient strength to allow its use as a source of supply in making the various official preparations of digitalis, and he concluded that by the use of ordinary methods in handling and preparing the leaves, a highly active product could be secured which compared favorably with the activity of cultivated leaves grown under more favorable conditions.

A new species of the American-grown plant, Digitalis lutea, has recently been employed and its efficiency tested on both animals and patients. White and Morris (139) have used this form of digitalis grown in Minnesota, and have compared its activity with Digitalis purpurea. They find that Digitalis lutea possesses the same therapeutic value as purpurea and seems to have less effect on the gastrointestinal tract. Christian (16) reports that he has had excellent clinical results with American-grown digitalis, and Pratt (122) who has used both American-grown purpurea and lutea, says that active leaves grow in various parts of the United States from Maine to the Pacific Coast.

Pratt and Morrison (123) tested out twenty-five samples of American grown digitalis by the one-hour frog method, using both purpurea and lutea. Their work shows that the best American digitalis, both wild and cultivated, is equal in activity to the best European digitalis. They obtained specimens of high potency from Virginia, Nebraska, Wisconsin, Minnesota, Oregon and Washington. There was, however, a definite difference in the potency of various samples, and seventeen out of twenty-five were below the standard of strength required by the United States Pharmacopeia. The average strength of the American-grown leaves was greater than that of the various imported leaves examined. Pratt and Morrison suggest that samples from a crop of digitalis should be tested biologically before it is gathered in large quantities for therapeutic use.

It may be considered as established that digitalis of good potency grows in America in both the wild and cultivated state so that dependence need no longer be placed upon the European market. The species Digitalis lutea seems also at least as useful as the Digitalis purpurea, and may prove to have some advantages over the better known species.

3. Strophanthus

This drug was introduced into medicine by Sir Thomas Fraser (55), who discovered it during an investigation of the arrow poisons used by certain African tribes. Several variations of the plant Strophanthus Kombé, S. hispidus, S. Gratus, and others contain the active principle of the drug, the seeds being especially rich in it, and are used in making the various preparations for therapeutic use. Hatcher and Eggleston (78) have pointed out the uncertainty of origin of much of the strophanthus of commerce, and state that they are not convinced that all commercial specimens of strophanthus—even those obtained from reputable dealers—are sold under their correct botanical names. This is perhaps more of an academic question than one of importance from the point of view of therapeutics, as the active principle, strophanthin, appears to be identical in its pharmacological properties, regardless of its source. Hatcher and Eggleston state that the active principle, strophanthin, has also been considerably confused. The term is properly employed only as

applied to amorphous strophanthin, but it has also been used for ouabain and "crystalline strophanthin-g." Ouabain is a crystalline substance obtained from strophanthus and represents the purest chemical substance, possessing the most potent activity of any body belonging to the digitalis group. It was isolated in 1888 from ouabain wood by Arnaud, who gave it its name and established its identity with that of the active substance obtained from Strophanthus gratus. This same substance was called by Thoms sixteen years later "crystallized strophanthus-g." As amorphous strophanthin and crystalline strophanthin or ouabain are both used therapeutically and may differ much in potency, this confusion of names is very unfortunate and should be avoided.

Strophanthus and its active principle possess all the pharmacological properties of digitalis, and the solubility and potency of strophanthin and ouabain make them important members of the digitalis group, being especially valuable for intravenous administration.

4. Other members of the group

Other members of the digitalis group have not a well established place in therapeutics, although some of them have been extensively used. Recently the action on man of several members of the group have been studied by modern methods by White and his collaborators. Squills, apocynum and convallaria have been administered to patients in whom the action of these drugs was compared with that of digitalis. These studies will be referred to when preparations are considered, but it may be stated at this time that they showed several reasons why these drugs are not as efficient as digitalis, and that they should not be used in the treatment of heart disease. Less is known about other members of the group. For these reasons the discussion of their action and their therapeutic use will not be included in this review.

IV. THE POTENCY OF THE DIGITALIS BODIES

1. The biological assay

The determination of the potency of a drug by quantitative chemical analysis is seldom feasible when the activity of the drug depends upon the presence of one and often of several chemically complex substances.

This has proved especially true of members of the digitalis group to which biological or pharmacological assays have long been applied. According to Hamilton (65) the earliest recorded attempt to standardize digitalis bodies by means of their effects when injected into animals was that of Fagge and Stevenson in 1866. In order to carry out the biological assay, the drug is administered to an animal in such a way that the amount necessary to produce a clearly defined and constantly occurring phenomenon can be accurately measured. By this method of assay the potency of various members of the digitalis group can be compared, and the various preparations for therapeutic use can be standardized.

A number of methods for the biological standardization of digitalis have been employed. Generally speaking, they depend on the determination of the minimal amount of drug required to kill the animal used. This method has been objected to as inapplicable to therapeutics as physicians do not want to kill their patients but to cure them. Hatcher (67) has made the following reply to this criticism:

> While it is perfectly true that physicians do not wish to kill their patients, it is equally true that the action of digitalis which they utilize in curing them is that which kills if it be carried too far, and it seems to me that it would be quite as logical to object to testing the strength of strands of cable by raising the tension to the breaking point, on the ground that engineers wish the cable not to break, as it is to object to the method in vogue for testing the activity of the digitalis bodies on the grounds mentioned.

There seems to be no better method of standardizing the digitalis bodies than that which depends on their power to kill.

The animals most commonly used for biological assays of digitalis bodies are the frog, the cat and the guinea pig, although the dog and the rabbit have been used by some experimenters, and one method has been suggested which depends on the determination of the minimal lethal dose for gold fish. The original method used by Fogge and Stevenson depended, according to Hamilton (65) upon the time required for the systolic stoppage of the exposed heart of the frog, after the drug was injected subcutaneously into the thighs. This general principle has been widely applied, and it has been recently especially elaborated and advocated by Focke (53). The frog test as employed

in 1916 (Roth, 136) by the Hygiene Laboratory of the United States Public Health Service, aims to determine the quantity of digitalis which will produce permanent systole of the ventricle, in an hour, when injected into the ventral lymph sac. Certain conditions, such as temperature at which the tests are carried on, the concentration of the injected fluid and its alcohol content, are kept constant. Roth states that a very disturbing factor in the one-hour frog method is that of absorption. The assay of digitalis by the frog method has been used with a number of modifications. In determining the minimal dose causing permanent systolic stoppage, the heart is necessarily exposed after the frog has been pithed, while in determining the minimal lethal dose this is not done. Hamilton (65) who has recently reviewed all the various methods of biological assay of digitalis that have been employed, apparently prefers the frog method and considers that there are advantages in determining the minimal lethal dose, namely, that less work and time are involved, that the factor of slow absorption is eliminated and that the end-point of the test is not obscured by rough handling necessitated by the pithing and laying bare of the frog's heart. However, in testing digitalis, it is not the general toxicity as much as the potency of the drug on the heart itself that is the essential feature, and therefore the systolic stoppage method with the heart exposed should be considered that giving the more exact information.

Hatcher and Brody (74) in 1910 proposed their cat method of standardization. This method determines the minimal lethal dose per kilogram of cat when the drug is injected slowly into the femoral vein. This amount, these authors have termed "the cat unit." For crystalline ouabain, the cat unit has been found to be 0.1 mgm., this amount of the drug per kilogram of cat being fairly constantly fatal when injected during a period of about ninety minutes. In testing other digitalis bodies Hatcher and Brody found that the accuracy could be increased by the following procedure. A measured amount of the digitalis body (tincture or infusion of digitalis, or digitoxin) is injected into the femoral vein in the first period of about ten minutes and after an interval of twenty minutes, the injection is resumed but a solution of crystalline ouabain is substituted for that of the digitalis body. This injection is continued slowly until the death of

the animal occurs. The difference between the amount of crystalline ouabain actually used to complete the assay and 0.1 mgm. per kilogram of animal (the amount which would have been required in the absence of the digitalis body) represents the activity of the digitalis used. There are certain precautions which the authors state, especially regarding the selection of animals, which should be followed. This method was adopted after the authors had assured themselves that ouabain was capable of replacing the other digitalis bodies.

The cat method is given in detail because of its increasing popularity especially with those administering digitalis accurately and carefully to patients. It is suitable for the standardization of the generally used therapeutic preparations, such as the tincture of digitalis, and can be carried out in any properly equipped laboratory, but its use by the retail pharmacist, as suggested by the authors, seems to the writer, to be, generally speaking, somewhat idealistic although highly desirable. The method has been criticized by Eckler (35) as complicated, time-consuming and expensive, and he points out a number of unknown factors that are involved, but he concedes that it has one point of superiority over all other methods in that the matter of absorption is entirely eliminated.

Macht and Colson (105) express as their opinion that the "cat method" gives more uniform results than the frog method, but they found that the fatal dose varies considerably in cats. They conducted two series of experiments: one in which the vagi were cut while the nerves were left intact in the other. Using digitalis, digitalin and strophanthin, they found that the results were more uniform in the series in which the vagi had been cut, but that the drugs were more toxic for these animals.

Hamilton (65) states that "the cat method is purely a toxicity test and can be classed with that on guinea pigs as objectionable because death is almost invariably due to paralysis of the respiratory center and therefore, not directly a measure of the heart toxic value." The experience of the writer with this method is not in accord with this statement. Respiratory changes practically always occur after the heart has ceased to beat, as revealed by the electrocardiograph. Auscultation of the cat's heart is also a helpful method of determining the end-point of the experiment, when digitalis is being injected intravenously.

Eggleston (41) has published a criticism of the cat method of Hatcher and has compared it with the twelve-hour frog method of Houghton, the one-hour frog method of Famuleuer and Lyons, and the guinea pig method of Reed and Vanderkleed. He discusses in detail the various factors which he considers important in the choice of a method for the biological standardization of the digitalis bodies. Eggleston concludes that there is no perfect or ideal method, but that each of the four methods discussed has certain advantages not possessed by the others. He considers, however, that the cat method of Hatcher possesses the greatest number of advantages which are as follows:

(*a*) It is accurate to within 10 per cent. (*b*) It gives constant results from year to year. (*c*) It provides a means of detecting the presence of deterioration. (*d*) It is the least affected by adventitious factors. (*e*) It tests the action of the drug upon which its therapeutic use depends. (*f*) It is not too difficult for general use. (*g*) It is neither time-consuming nor too costly. (*h*) By it, widely different preparations can be compared accurately. (*i*) Its results are transferable to man. (*j*) It has the widest range of applicability of all the methods.

Neither the frog nor the guinea pig method fulfils so many of the essential requirements as does the cat method. The cat method fails in no single requisite and has far fewer disadvantages than any other method yet proposed.

Another advantage which the cat method of standardization seems to the writer to possess over the frog method may perhaps be described as psychologic. It is easier to think of dosage in terms of cat units than it is in terms of frog units. Hatcher and Brody quote Focke as saying that he believes it is not feasible to accustom physicians to thinking and calculating the strength of digitalis preparations in frog units. On the other hand, the cat unit strength of the various forms of digitalis is becoming widely accepted. The figures are larger and therefore more nearly approach the therapeutic doses, and they also tend to fall into certain multiples which make them readily applicable for calculations of dosage. Eggleston is of the opinion that the relative toxicity of the various digitalis bodies for the cat corresponds more accurately to the relative potency of these drugs for man than does their toxicity for the frog or guinea pig.

It is very desirable that all forms of digitalis should be biologically assayed by a uniform method, preferably by the cat method for reasons that have been given. The strength of every preparation put upon the market should be indicated preferably in terms of the cat unit, and the date of manufacture and of assay should be stated. In the case of some preparations, and probably in many, the strength of the drug can be adjusted so that a fixed amount has a constant strength. For example, 1 cc. of the tincture should always represent 1 cat unit no matter by whom it is manufactured. This adjustment of strength is very desirable. When this becomes a uniform procedure, the medical profession will learn to use the preparations of digitalis according to their individual potency, and not follow a rule of dosage which may have but little bearing on the preparation being used.

Even though the strength of a preparation of digitalis, as determined by the biological assay method is known, the physician should always study the relation between the amount of the drug given to patients and its effect upon them. He should endeavor to determine the average amount of every preparation that is used necessary to produce well defined digitalis effects. If opportunities are afforded for doing this adequately, as can be obtained in modern hospital practice, perhaps the best method of digitalis standardization for practical purposes is available.

2. The relative potency of the digitalis bodies

The potency of a number of the more important members of the digitalis bodies was determined by Hatcher and Brody (74) and later Hatcher (68) repeated some of this work, correcting a few of the figures reported with Brody. From these two papers the relative potency of these drugs may be tabulated, the number of milligrams of the drug which represents 1 cat unit, or the number of milligrams which is the fatal dose for the cat on the basis of 1 kilogram of body weight of the animal, being used to express their potency.

	mgm.
Ouabain, crystalline	0.10
Strophanthin, amorphous, Boehringer and Sons	0.13
Merck	0.17
Digitoxin, crystalline	0.30 – 0.50
Digitoxin, so called amorphous	1.20
Digitalinum verum, Kiliani	1.50
Adonidin	3.00
Strophanthus, Kombé	3.00
Digitalein	3.50
Digitalin, German	3.60
Digitalis, German	82.00
Digitalis, English	92.00

This table indicates clearly the relative potency of the three active principles of digitalis, digitoxin, digitalin and digitalein, and shows also the relative toxicity of ouabain and amorphous strophanthin.

3. Variations in potency

The varying strength of the preparation of digitalis has been a problem which has caused much uncertainty and discussion. It has confused the question of dosage. The chief sources of the difficulty have been variations in the digitalis content of different specimens of leaves, deterioration and probably variations in absorbability from the gastrointestinal tract. Roth (136) found that in 1916 the methods of biological standardization employed by American drug manufacturers were not uniform and, in some instances, manufacturers were not carrying out a biological standardization of their digitalis products.

Pratt (12) was among the first to show the inefficiency of some of the digitalis on the market. By using the thirty-minute frog method he assayed nine samples of digitalis leaf obtained from leading apothecaries and hospitals in and about Boston, and found only one strong digitalis leaf among the number. A sample obtained from Germany prepared and standardized by Caesar and Loretz proved to be twice as strong as the best leaf obtainable in the American market. Pratt concluded that the available tinctures were also low in potency, as he was unable to obtain the therapeutic results with them which were immediately obtained in the same patients when good powdered leaves were used. Goodall, according to Fulton (56), examined a number of tinctures of digitalis over a period of three years and found

that during this time, nearly half the number had departed from the standard strength, the limit of variation being from 275 per cent over-strength to 40 per cent under-strength. Goodall found that the tincture was apt to deteriorate within a year. The writer found that one lot of the tincture kept in the drug room of a hospital in a 5-gallon container, and which had a cat unit of 1 cc. when first tested, had deteriorated so that the cat unit was approximately 2 cc. at the end of one year.

Roth (136) found by the one-hour frog method a variation of over 250 per cent in the thirteen samples of commercial "fat-free" tincture of digitalis and a variation of 150 per cent in five samples of German commercial digitalis. No definite reason could be given for the initial variations in the samples of the fat-free digitalis.

Newcomb and Rogers (115) who also found differences in the strength of various preparations, consider that the chilling of the tincture of digitalis to a temperature of 40°F., even for a brief period of time, causes an increase in the natural precipitation, which carries down some of the active principles of the drug.

On account of the opinion prevalent among physicians and pharmacists that digitalis and its preparations undergo deterioration with considerable rapidity, Hatcher and Eggleston (76) reviewed this subject and undertook an investigation on the keeping properties of digitalis and some of its preparations. The cat method and, in some instances, the one-hour frog method were employed for estimating the activity of the specimens. They used samples of leaves, ground and unground, tinctures, extracts and fluid extracts ranging from less than one to more than thirty years old. Their findings do not confirm the common belief regarding deterioration, as they found that commercial digitalis leaves of good quality do not undergo any deterioration in many instances as the result of age. In a few cases they do appear to have deteriorated but only with extreme slowness—at a rate probably not exceeding 1.5 to 2 per cent a year. Although the presence of moisture has been emphasized as a cause of deterioration, several of their specimens of leaves had not been protected from moisture. Mouldy leaves, however, must be considered as worthless. Pharmacopial preparations made with a menstruum containing at least 50 per cent alcohol showed no greater deterioration than the

leaves. Of course, the infusion of digitalis is notoriously unstable and those using it carefully usually insist on its preparation within a few days of its administration. Hatcher and Eggleston (77) studied the stability of the infusion, using the same methods employed in their previous work. The most striking facts shown by their experiments are that an infusion of digitalis made without alcohol and kept without the least care, in fact under more unfavorable conditions than should obtain in practice, may retain its activity with little impairment for periods varying from six to nineteen days; and that when the hot infusion is bottled with reasonable care, it will often keep practically unchanged for many weeks even during the summer.

The stability and constancy of the purer substances, such as the single glucosides and especially the crystalline substance such as ouabain would be expected to render them above reproach, from the point of view of stability. But such is not the case. Sollman (142) has pointed out several factors, especially variations in temperature and concentration of the solution which affect the toxic dose of ouabain in frogs, and which may cause errors in the biological assay of the drug. Deterioration of crystalline strophanthin has been found by Levy and Cullen (95) in the preparations marketed for therapeutic purposes. They studied the cause of this deterioration and propose a well founded remedy for it. Many of the glass containers commonly used in the laboratory and most of the glass ampules employed in marketing sterile solutions for hypodermic or intravenous medication yield sufficient alkali on autoclaving to change the reaction of distilled water from pH 6 to pH 9. This increase in alkalinity is sufficient to render biologically inert and practically to decompose aqueous solutions of crystalline strophanthin in the concentration employed in clinical medicine. Levy and Cullen suggest that for clinical use crystalline strophanthin be dissolved in 0.02 M standard phosphate solution at pH 7 and marketed in hard glass ampules, thereby insuring stability of reaction and preservation of the biologic activity of the drug. This work views the question of deterioration of the digitalis bodies from a new angle, from which the deterioration of some of other members of the group should be studied.

The relative potency of the tincture of squill when administered orally as compared with the tincture of digitalis is shown by the recent

work of White, Balboni and Viko (158). They investigated the effect of a standardized tincture of squill on the hearts of a series of patients and found that although squill has a definite digitalis-like action on the heart, it appeared only after doses eight to sixteen times as large as those generally recommended. These observations confirm the opinion of Cushny (30) that, considered clinically, squill has only one-half or one-quarter the effect of digitalis.

The question of absorption from the gastro-intestinal tract is one that complicates the problem of the effects which the various digitalis bodies exert when administered by mouth. As it is not primarily a matter of the relative potency of the various members of the group, it is best discussed after the question of dosage has been taken up.

V. ANIMAL EXPERIMENTATION

The effects of digitalis and its allies on animals have been studied by many investigators and there is an extensive literature on the subject. Those studies in which mammals have been used have furnished the more valuable results from the therapeutic point of view, and some of these studies will be reviewed. These experiments have served as a basis for the analysis of the effects observed in man during the so-called empirical period of the use of digitalis, and they have also pointed the way to the improvement in methods of administration. They have been of great value in rationalizing the therapeutic use of the drug, so that today a fair degree of scientific accuracy is possible in regard to its use. On the other hand, animal experimentation has too strongly dominated the ideas concerning the results to be expected when the drug is administered to patients with heart or circulatory disease.

As Cohn (20) has pointed out, Schmiedeberg and his pupils have emphasized, that the main action of a digitalis body is on the heart muscle; while the school of Gottlieb has been particularly interested in the effects the drug has on the blood vessels, and maintains that it has an important action on the walls of the arteries. "Both schools find that the drug increases the excursion of the heart in contraction, both believe that it elevates blood pressure, both believe that it increases the amount of renal secretion." Recent observations on patients by methods which allow an accuracy closely approaching

that of animal experimentation, make it necessary to readjust our ideas, as the predominating effects on patients on which the beneficial results of the drug depend are not those predicted by animal experiments. The careful clinical observations of Cohn have been of importance in bringing out this point, and he says:

> It is perhaps not an overstatement to say that in a general way clinicians have been too much influenced by these experimental results and have felt obliged to find that the administration of the drug in patients results in parallel phenomena. It requires a very small experience in treating patients suffering from heart disease to find one's self disappointed because the expected results did not occur. And when discrepancies were noticed, the discovery was not often followed by an effort to explain them, the subject was often dismissed by finding fault with the potency of the drug or by discovering an idiosyncrasy in the patient. But even if drugs were always potent and there were no individual idiosyncrasies, it is extremely likely that patients would continue to react in different manners to the drug. And the reason for that must be that individuals, although they suffer from what, in a general sense, is called heart disease, yet present a great variety of clinical pictures.
>
> There can be no question of the usefulness to therapeutics of these experiments; as guides, they are indispensable, but it must be clear that they neither replace nor parallel the clinical conditions we must treat. That there has consequently been a divergence between the results of the pharmacologists and clinicians in a practical sense is inevitable. The responsibility for it is probably shared equally by both. Pharmacologists have dealt usually with simple normal conditions; clinicians with complex pathologic ones.

This review attempts to emphasize the recent careful studies of the effects of digitalis on patients and gives preference to the work from the clinic over that from the laboratory, when the clinical studies are such as to justify this preference. The more exact clinical studies of digitalis were inaugurated by Mackenzie (107) and he was perhaps the first to point out in 1911 that the clinician must exercise great judgment in the application of pharmacological knowledge in the treatment of his patient. The confusion of results from the laboratory and of those from the clinic is caused mainly by the fact that observations have been made on widely different species and that great differ-

ences in dosage have been employed. Uniform criteria have not been employed, and the tissues on which the drug acts have not been exactly ascertained.

The most important statement regarding the question of the value of animal experiments on the therapeutic use of digitalis is that made in 1918 by Cushny (31) one of the foremost experimentalists with digitalis. He said:

> More than a century after the introduction of digitalis, the knowledge of its therapeutic action had made but little progress and was meagre and unsatisfactory, because no accurate knowledge of the clinical action was attainable, and the facts of the laboratory could not be confirmed for man.

Cushny who studied patients with Mackenzie has done much to introduce the new chapter in the study of digitalis, the chapter of exact clinical observations. In his important experimental work, published in 1897, he employed a method which was a forerunner of one of the clinical methods that have thrown much light on the problem of digitalis action. Cushny (28) studied the action of the drug directly on the heart of the dog and observed, by means of the myograph the action of the auricles and ventricles separately, thus making it possible to differentiate the various forms of disturbed cardiac mechanism which have become so important in the clinical study of the drug.

VI. THE NEWER METHODS OF CLINICAL STUDY OF DIGITALIS

The newer methods may be put into two groups. In the first group belong those methods that give accurate information regarding the movements of the various parts of the heart. In the second group, may be put the quantitative clinical methods such as the accurate measurement of the intake and output of fluids, the quantitative estimation of kidney function, the measurement of blood pressure and of the vital capacity of the lungs, together with the variety of useful procedures that have been developed by the application of biochemistry to clinical medicine. All of these methods have been used, not only directly in the study of digitalis in man, but they have also served to differentiate with greatly increased accuracy the many conditions belonging to the general class of heart and circulatory disease, and have so added a degree of specificity to digitalis studies which was hitherto impossible.

The introduction of the polygraph by James Mackenzie inaugurated the methods by which the movements of the auricles and ventricles of man can be studied separately, and by which the efficiency of the mechanism conducting the cardiac impulse from one chamber of the heart to the other can be determined. The value of this method is demonstrated by the masterly studies of digitalis published by Mackenzie (106, 109) in 1905 and 1911 which have added much to our knowledge of the action of the drug in heart disease.

The adaptation of the string galvanometer by Einthoven furnished the second great advance in this direction, and the electrocardiograph has added much to the modern concepts of digitalis action in man. In it we possess a method that not only clearly differentiates all the disturbances of cardiac mechanism, but which also gives us information of importance regarding the direct action of digitalis on the heart muscle, allows the detection of very early toxic effects of the drug on the heart, and serves as an aid in determining pathological conditions of the myocardium.

Although these two methods are not perhaps as yet available to all practicing physicians, the information which they yield is translatable, as Christian (14) remarks "into the terms of general practice, that is, brought into the range of such observations as is possible with fingers, eye and stethoscope."

Of the methods belonging to the second group, comment is necessary perhaps in only one instance, namely the measurement of the vital capacity of the lungs as a means of studying the effect of digitalis. Several years ago, Peabody showed that the vital capacity of the lungs (the amount of air, measured by a spirometer which can be forced from the lungs after the deepest possible inspiration), varied directly with the efficiency of the circulation. He also showed that normal individuals of the same sex, weight and height gave vital capacity readings of sufficient constancy to allow the establishment of a normal standard. West and Pratt (156) have recently reported a series of cases to which digitalis was administered and in which the vital capacity of the lungs was taken as one of the criteria for the estimation of the effect of the drug. Although it is not entirely clear how the improvement of the circulation causes an increase in the vital capacity, the method holds promise as a means of estimating quantita-

tively the functional efficiency of the circulation, and may therefore fulfill, at least in part, one of the greatest needs in the study of the effect of digitalis in heart disease. This method, the technique of which is quite simple, should be included in all comprehensive studies of the effects of digitalis on man.

VII. THE TOXIC EFFECTS OF DIGITALIS

In considering the effects of digitalis on man, they are naturally separated into those that are advantageous and those that are deleterious, especially to patients suffering from heart and circulatory disturbances. These two groups of effects may be spoken of as the therapeutic and the toxic effects. In most instances, the two groups can be separated by the ultimate results of each on the circulation as a whole, but sometimes the prevailing conditions of the circulation may make this separation somewhat difficult, as effects which would be considered toxic, under most circumstances, may have, under some conditions, therapeutic value. Therapeutic and toxic effects may also occur simultaneously when the drug is being administered in large doses to patients, and the close relation between the optimum therapeutic dose and that producing early toxic symptoms presents one of the greatest problems involved in the skilful use of the drug in therapeutics. For instance, Bailey (quoted by Bastedo (5)) found that of ninety patients in Bellevue Hospital taking digitalis, about 25 per cent showed one or more toxic effects of the drug.

The characteristic effects of all members of the digitalis group are those on the heart and on the central nervous system, but in order to understand the action of these drugs so that they may be intelligently employed in the treatment of disease, a close analysis of their effects must be made and careful consideration must be given to the various pathological conditions they may be expected to benefit.

The first requisite for the successful employment of digitalis as a remedy is the recognition of its toxic effects, especially of those early effects which serve as indications for the discontinuance of the drug. For this reason the deleterious or toxic effects of the drug will first be discussed.

1. The gastric effects

In the earliest accounts of digitalis, reviewed by Withering (163), the effects of the drug on the gastro-intestinal tract were described, and it was spoken of as a poison having an emetic and a purgative action. All modern study of digitalis has taken into account the gastric symptoms, loss of appetite, nausea and vomiting which constantly follow the use of all members of the digitalis group in large doses; and they have been recognized as among the earliest toxic symptoms which the drug produces.

Anorexia, nausea and vomiting are symptoms observed by all who have used digitalis in sufficient doses, as they are probably the commonest of the "side-actions" as Eggleston puts it, encountered in the clinical use of the digitalis bodies.

The peculiarities of the emetic action of digitalis were noted by Withering (163) who wrote:

> It is curious to observe that the sickness, with a certain dose of this medicine, does not take place for many hours after its exhibition has been discontinued. . . . . The sickness then excited is extremely different from that excited by any other medicine; it is peculiarly distressing to the patient; it ceases, it recurs again as violent as before; and then it will continue to recur three or four days at distant and more distant intervals.

Vomiting should be avoided if possible, especially when digitalis is being given to patients with severe symptoms of heart failure. This is an important reason for the recognition of the earliest toxic effects of the drug, in order that it may be stopped before the onset of vomiting. As Pratt (122) says,

> Vomiting may be preceded by a day or two of complete anorexia, which should be a sign for the immediate discontinuance of the drug, when it seems evident that the anorexia is caused by the digitalis. It is then an indication that the so-called physiologic limit has been reached, and that nausea and vomiting will follow if more digitalis is given. The stoppage of the drug at the first appearance of anorexia does not always prevent vomiting, but it does not, as a rule, last more than a few hours under these conditions. When the drug is administered until vomiting actually occurs, nausea and vomiting may be present for two or three days and occasionally for a week, passing off and recurring several times, even after the drug has been stopped, as Withering observed.

A difficulty in avoiding nausea and vomiting during digitalis administration is the fact that in some cases, the desired effects of the drug on the heart are obtained with the same dose as that producing the gastric symptoms. Mackenzie (107) noted in his cases that the cardiac effects usually preceded the gastric symptoms, but the two occurred synchronously at times, and Cushny (30) states that minor toxic symptoms, loss of appetite, headache, nausea and vomiting and often diarrhoea usually accompanied the improvement of the circulation produced by the drug. Clinical judgment is the only guide in dealing with individual cases which present this dilemma. Confusion sometimes arises in patients whose stomachs are in a highly irritable state, as is not infrequently seen in heart failure, and who vomit when anything is taken into the stomach. Such patients will often vomit within a few minutes after a dose of digitalis, and then it is safe to say that the drug is not responsible for the vomiting. The reason for this statement will become evident when the mechanism of the emetic action of the digitalis is discussed. Such vomiting should not be taken as a sign for the discontinuance of the drug, as the gastric symptoms may disappear with an improvement of the circulation. A method of administration other than oral may have to be resorted to, however, in such cases.

The relation of the therapeutic use of digitalis to nausea and vomiting has been studied by Eggleston (40) in a series of 15 patients, all of whom were suffering from heart disease. Digitalis was given in the form of the infusion or tincture in the usual or slightly larger doses, as a rule, every four hours. Eleven cases were instances of auricular fibrillation. In this series nausea alone, or nausea and vomiting developed on an average of five days from the beginning of the digitalis administration, when an average of 3.08 grams, corresponding to $7\frac{3}{4}$ drams of the tincture had been taken. In the 4 cases with regular cardiac rhythm, nausea or vomiting occurred in seven days, after the average dose of 2.4 grams of the drug had been given. The average dose in these cases was smaller than that given to the patients with auricular fibrillation. In none of the 15 cases did the onset of nausea or vomiting bear any constant time relation to the administration of the individual doses of the drug. In most cases nausea or vomiting persisted or recurred for some hours after the last dose had been given and the drug withdrawn.

In estimating the total amount of digitalis which will, on an average, lead to nausea and vomiting, the question of elimination of the drug during the days of its administration must be taken into account, and only rough estimates can be made which have any value when applied generally to patients. Large single doses of digitalis were administered to about 100 patients by Robinson (130), the doses usually ranging from 15 cc. to 25 cc. of a standardized tincture, or 1.5 to 2.5 grams of digitalis. The patients were all adults, and suffered from a variety of cardiac disorders. Only about 10 per cent of these patients showed the toxic gastric symptoms caused by digitalis. Nausea and vomiting came on in these cases in from one-half to one hour after the large doses had been given. Eggleston (40) has collected and tabulated 95 cases from the literature to which digitalis bodies were given in the usual doses until nausea or vomiting appeared. The cases of this series were divided into three groups. The first consisted of cases of auricular fibrillation, the second group of non-fibrillating cases and the third group receiving digitalis bodies other than the leaf. In reviewing the first two groups, it is seen that the dose of digitalis producing nausea or vomiting varies from 1.25 grams to 8.50 grams and the figures are not sufficiently constant to warrant an average of significance to be obtained from them. The dosage falls, however, most often between 2.5 grams and 3.5 grams. A comparison of these two groups of cases leads to the conclusion that the type of heart disease has no direct influence on the amount of digitalis required to produce gastric symptoms, which occur also with approximately the same doses in individuals with normal hearts. The analysis of cases of the third group shows that crystalline digitoxin (Nativelle's digitalin granules), tincture of strophanthus and of squills, and the extract of apocynum also cause nausea and vomiting, when given in sufficient doses. Cushny (30) concluded from clinical observations that digitalis had perhaps less effect on the gastrointestinal tract than strophanthus and squills.

The mechanism by which the digitalis bodies produce their emetic action has been only recently clearly demonstrated, although much speculation and some experimentation had been carried on regarding it. In 1912, Hatcher and Eggleston (75) pointed out that the emetic action of the drug had been generally attributed to its irritant action

on the gastric mucosa, but that there were several discrepancies between the deductions which had been drawn from animal experiments and the occurrence of nausea and vomiting in patients receiving therapeutic doses of the drug. They observed that the digitalis bodies, as a rule, produced emesis more rapidly and with smaller doses when given intravenously than when introduced into the stomach. In order to eliminate the possibility of action of the drugs during excretion from the blood stream into the stomach, digitalis and several of its allies were injected intravenously into dogs from which the gastro-intestinal tract had been removed. Sixteen of the 21 eviscerated animals went through the motions of vomiting, after the injection of these drugs, and three others showed signs of severe nausea. They injected digitalis, digitoxin, true digitalin, ouabain, strophanthus, amorphous strophanthin and adonis. Hatcher and Eggleston conclude from their experiments that the emetic action of these drugs is exerted upon the vomiting centre in the medulla and is not caused by the local irritation of the gastric mucosa. They consider the purgative action also as obviously of central origin.

Recently the report of Hatcher and Weiss (78 a) on the emetic action of the digitalis bodies has appeared in a preliminary form. They state that Thumas has shown that the direct application of the digitalis bodies to the vomiting centre in the medulla does not cause emesis. By means of a series of experiments on cats in which various nervous structures were cut, Hatcher and Weiss have shown that digitalis causes emesis only when the nerve supply to the heart is intact. The vomiting centre is not stimulated directly, but by impulses reaching it from the heart, passing up by way of the sympathetic, and to a less, though probably variable extent, by way of the vagus. Ouabain usually failed to produce vomiting after the sympathetic only was cut.

These investigators consider their experiments as evidence that the digitalis bodies induce emesis by reflex action due to irritation of the heart or its appendages. The effect they consider as almost certainly a protective mechanism for the heart such as is recognized in the case of other organs. With the establishment of the fact that emesis is not an effect produced by the direct action of digitalis on certain structures of the medulla, but is secondary to the direct

action of the drug on the heart, a new attitude must be taken regarding its relation to the cardiac effect of the drug. The effect of the drug on the heart and its effect in producing nausea and vomiting cannot be dissociated and the latter would seem to have a more significant place than has been given to it in evaluating the cardiac action of digitalis.

In a second paper Eggleston and Hatcher (48) investigated the relative emetic activity of a number of more commonly used digitalis bodies and also of several proprietary preparations for which diminished emetic action was claimed. They determined the percentage of the fatal dose required to produce emesis in cats when injected intravenously. The minimal dose and the average of the emetic doses of various digitalis bodies and specialties in percentage of the minimal lethal dose of each drug are given in their paper as follows:

DRUG OR SPECIALTY	EMETIC DOSE IN PERCENTAGE OF FATAL DOSE	
	Minimal	Average
True digitalin	18	22
Strophanthus	27	47
Ouabain	30	49
Digitalis	31	46
Crystalline digitoxin	40	58
Amorphous strophanthin	61	65
Digipuratum	25	42
Fat-free tincture of digitalis	28	34
Digitalysatum	29	36.5
Digalen tablets	29	40
Digalen, liquid	30	38

Eggleston and Hatcher have shown therefore that all these digitalis bodies and preparations have an emetic action which do not differ quantitatively very markedly. True digitalin is the most active emetic, while amorphus strophanthin and digitoxin are the least active in percentage of their fatal doses. There is very little difference between digitalis and various specialties, and these experiments furnish no evidence that digalen, digipuratum, digitalysatum and the fat free tinctures have any advantage over the less expensive galenical preparations of digitalis from the point of view of being

less disturbing to the stomach when used therapeutically. These authors conclude that there is at present no means of securing the cardiac action of the digitalis bodies without subjecting the vomiting centre to the influence of these agents at the same time, and there is no advantage in substituting one mode of administration, or one member of a group for another, in an attempt to prevent or lessen the gastric symptoms which these drugs cause. They also express their disapproval of the employment of opium as has been advocated to prevent the gastric symptoms, as it may serve to mask the toxic symptoms which should serve as a signal for the discontinuance of the drug or the reduction of the dose.

These experimental studies were followed by the clinical study of Eggleston (40) to which reference has already been made, and in which he correlated clinical experience with the facts of the experiments. He showed in his own series of 15 cases and in 95 cases from the literature, nausea and vomiting almost never occur as a result of digitalis until it had been absorbed sufficiently to produce its characteristic effect on the heart. His study shows that there is no valid evidence that therapeutic doses of the digitalis bodies cause nausea or vomiting through local irritation on the alimentary tract, but that there is strong evidence to the contrary. He concludes, therefore, that the nausea and vomiting resulting from the therapeutic use of digitalis and its allies in man are due to their direct action on the vomiting center in the medulla. Eggleston draws the deduction from his conclusions that preparations which fail to produce nausea and vomiting when administered in large doses are either weaker than those that do produce these effects or are less well absorbed.

Vomiting may be considered as a desirable effect from one point of view, as it may prevent further toxic symptoms from following an overdose of the drug when taken by mouth, as part of the drug may be eliminated when the stomach is emptied by the vomiting which it produces.

The purgative action of digitalis has not been prominently described in recent clinical studies, and its absence was noted in the 42 patients carefully studied by Mackenzie (107) to whom sufficient digitalis was given so that gastric symptoms usually occurred. He found,

however, that diarrhoea was produced by strophanthus and squills. Bastedo (5) also noted that diarrhea is much less frequent than anorexia, nausea and vomiting as a sign of overdose in digitalis administration. The writer's experience confirms these statements.

2. The toxic effects on the heart

Although the gastric disturbances are the most obvious unfavorable effects of digitalis, the cardiac disturbances must be regarded as the most serious in the clinical use of the drug. It is the direct effect of digitalis on the heart which produces death in animals to which a lethal dose is administered, and certain disturbances of the heart-beat resulting from an overdose of the drug to man must always be considered as the forerunner of effects which profoundly lower the efficiency of the circulation and which render the heart eventually incapable of maintaining the circulation. For this reason, the early recognition of the unfavorable effects of the drug on the heart is a matter of paramount importance.

When Cushny (28) first studied the effect of digitalis on dogs by a method that allowed the activity of auricles and of ventricles to be distinguished in graphic records, he discovered early effects which he attributed to the stimulating action of the drug on the vagus centre and later effects which he considered as the result of the direct action of the digitalis on the heart muscle. These later effects, constituting the second stage of digitalis action, were attributed mainly to an increase in the irritability of the myocardium.

Robinson and Wilson (134) administered digitalis intravenously to cats and followed the effect of the drug on the heart by electrocardiograms. It was found that when about 75 per cent of the lethal dose was administered, evidence of increased irritability of the ventricles appeared, manifesting itself as premature contractions which were soon followed by idioventricular rhythm, when cardiac impulses were being generated at a more rapid rate in the ventricles than in the auricles. This state of affairs was followed, during further administration of the drug, by ventricular fibrillation and death.

More recently Levine and Cunningham (94) using the same methods have found that when various preparations of digitalis were injected

into cats, premature ventricular contractions or extrasystoles appeared when an average of 48 per cent of the lethal dose was administered, and they considered the appearance of this phenomenon to mark the onset of increased ventricular irritability. They used the appearance of ventricular extrasystoles therefore as evidence of the first toxic sign of digitalis.

The analysis of unfavorable effects of the drug on the heart when administered to man had its inception with the first of Mackenzie's studies published in 1905, when he described the bigeminal pulse and recognized that its production resulted from frequent ventricular extrasystoles. He also showed that the conduction of the cardiac impulse is disturbed by the drug. In 1911, Mackenzie pointed out that digitalis may cause irregularities of impulse production, extrasystoles, partial heart-block, and pulsus alternans. The cardiac manifestations of overdose in digitalis administration were studied by Bastedo (5) who made polygraphic records of patients receiving the drug, and demonstrated the occurrence of auricular and ventricular extrasystoles, partial heart-block, paroxysmal trachycardia and possibly pulsus alternans. Bastedo recommends that digitalis be discontinued whenever the radial impulse rate goes below 60 per minute, whenever sudden slowing of the heart rate indicates the occurrence of heart block, whenever a regular ventricular rhythm becomes irregular, whenever tachycardia occurs or whenever coupled rhythm or phasic arrythmia appear in hearts showing auricular fibrillation.

a. Premature contractions. The two outstanding disturbances of the cardiac mechanism which digitalis causes in patients are those resulting from increased irritability of the ventricles and from depression of the conduction of the cardiac impulse from auricles to ventricles. The effect of digitalis on the ventricles leads to the occurrence of *premature contractions* of ventricular origin, commonly called extrasystoles. They are, generally speaking, always detrimental to the efficiency of the heart. Premature ventricular contractions tend to occur in diseased hearts and are, in many patients needing digitalis, readily provoked by relatively small doses of the drug. They appear to be provoked especially readily in patients with auricular fibrillation, when coupled rhythm replaces the absolutely

irregular cardiac action. At times these premature beats occur so frequently after small amounts of digitalis that it is the better part of judgment to discontinue or diminish its use before the optimum therapeutic effects are obtained.

The occurrence of ventricular premature beats may be readily recognized by the stethoscope with the finger on the pulse when they occur in hearts beating otherwise regularly. Except when definite coupled beats occur, it is impossible to recognize premature ventricular contractions however in cases of auricular fibrillation without electrocardiograms, which alone show, by the variations in form of the ventricular complexes, that some of the cardiac contractions are arising from ectopic points in the ventricles. The frequent occurrence of ectopic ventricular contractions during the use of digitalis in auricular fibrillation may be sometimes responsible for the failure to get the ventricular slowing that the drug usually produces in these cases.

There is a great difference in patients as to the amount of the drug which causes the onset of premature ventricular contractions, and no statement as to the average amount required can be made. It is evident, however, that in many patients ventricular contractions occur with an amount of the drug which is a much smaller proportion of the lethal dose than has been observed during the intravenous administration of the drug to cats.

Edens and Huber (38) have discussed the production of premature ventricular contractions by digitalis, and the occurrence of the bigeminal pulse. They consider it probable that the bigeminal pulse follows the administration of digitalis only in hypertrophied hearts with lowered muscular efficiency. They believe that the production of the bigeminal pulse by digitalis is an unfavorable prognostic sign. They also point out the great variability in the size of the dose which brings about the bigeminal pulse. Although their ideas regarding the relation of cardiac hypertrophy and inefficiency to the digitalis bigeminal pulse have not been confirmed, it is a point worthy of close attention.

The frequency of apparently spontaneous premature beats may lead to some difficulty in fixing the responsibility for them during digitalis administration, but it should be emphasized that it is a

definitely established fact that they may be caused directly by digitalis, and should always be considered as a probable toxic effect whenever they occur during the administration of any member of the digitalis group. The influence of digitalis on apparently spontaneous premature contractions will be discussed later.

The production of the so-called auriculo-ventricular rhythm by digitalis is an effect of the drug closely related to the production of premature ventricular contractions. This type of disturbed cardiac mechanism has been observed by Cohn (20) to follow the administration of digitalis and to disappear when digitalis had been completely eliminated. In auriculo-ventricular rhythm, the auricles and ventricles beat independently but each at nearly equal rates. Electrocardiograms indicate that the auricular stimulation is not usually disturbed, while the auriculo-ventricular node (of Tawara) assumes the rôle of ventricular pace-maker, by generating stimuli at a slightly faster rate than the sino-auricular node. Auriculo-ventricular rhythm is associated only with various forms of cardiac intoxicants, notably digitalis.

b. Depression of conduction of the cardiac impulse from auricles to ventricles is one of the most striking effects of digitalis, which may lead to partial or complete heart-block. This action of the drug is generally considered to result, for the most part, from its stimulating effect on the cardio-inhibitory mechanism, although there is not entire agreement as to the relation of this effect to the direct action of the drug on the cardiac tissues.

The great value of digitalis in certain forms of heart disease depends largely upon its ability to block impulses in their passage from auricles to ventricles, and for this reason the action of digitalis on conduction will be discussed when the therapeutic effects of the drug are considered. On the other hand, heart-block produced by the administration of digitalis may definitely lower the efficiency of the circulation and it must be considered therefore as a toxic manifestation of the drug. Its recognition and the means of avoiding its production will be briefly discussed at this time.

Mackenzie (106) first demonstrated heart-block as an effect of digitalis in man in 1905. Since that time, the influence of digitalis on conduction has been extensively studied by graphic methods.

As Bastedo (5) has pointed out, when a rapidly beating heart becomes suddenly slowed during the administration of the drug or if an intermittent cardiac rhythm unassociated with premature beats develops, it is safe to infer that heart-block exists. These events should be taken as indications for discontinuing the administration of digitalis.

Uncertainty of the diagnosis of heart-block will always exist, however, without the employment of the polygraph or the electrocardiograph. It is only by these methods that the earlier effects of digitalis on conduction, when the cardiac impulses are merely delayed in their passage from auricles to ventricles, can be detected. It is distinctly advantageous, therefore, to employ these methods during the administration of digitalis in order to detect its effect on conduction before a stage is reached which may lower the efficiency of the heart.

A number of students of digitalis, among whom are Edens (37) and Cushny (29) have expressed the opinion that digitalis affects especially the conducting system of hearts in which the auriculo-ventricular conduction has been previously damaged by disease. Although Cohn and Fraser (22) have shown that this is by no means a necessary condition for the production of digitalis heart-block, it must be a predisposing factor in some instances. It is very desirable to know the functional state of the conducting system before the administration of the drug to patients with heart disease, and this information is furnished by measuring the time between the onset of auricular activity and ventricular activity. When this time is found delayed beyond the normal limits, it should be taken as a contraindication for the use of digitalis or it should call for caution, careful observation, and alteration of dosage.

R. H. Halsey (64) has reported a case showing profound effects brought on apparently by excessive vagus stimulation producing severe subjective symptoms. Following the administration of digitalis to a patient with auricular fibrillation, severe cardiac failure and Cheyne-Stokes breathing, marked variation in the ventricular rate from 100 to 50 beats per minute were observed, the rapid rate occurring during the periods of apnea. This phenomenon apparently interfered with the interchange of O_2 and CO_2, and was relieved by atropin when the ventricular rate became 150 per minute.

Windle (161) studied the comparative effects of digitalis, strophanthus, squill and apocynum on the conduction of cardiac impulses in a case of mitral stenosis which required treatment on four occasions. He used a different drug each time, the tincture of each being employed. Apocynum had no effect on conduction, while the other three drugs caused partial heart-block with approximately equal amounts.

> 630 minims of the tincture of digitalis were given in 14 days
> 540 minims of the tincture of strophanthus were given in 19 days
> 480 minims of the tincture of squill were given in 4 days.

Heart-block was observed in each instance. It is evident that these three members of the digitalis group required total amounts which are comparable to produce partial heart-block in this case, although the rate of administration was different.

c. Other disturbances of the heart beat have been observed occasionally following large doses of digitalis. The auricles are affected, although less frequently, in the same manner as the ventricles, and premature auricular beats sometimes occur during the digitalis administration, presumably as a result of the action of the drug. Bastedo (5) has reported a case of paroxysmal tachycardia which he considered as produced by digitalis, but the relation of the inception of this disturbed cardiac mechanism and the action of the drug seems uncertain.

Special interest is attached to the influence digitalis may have in causing auricular fibrillation. Cushny (30) has stated that digitalis may cause the onset of auricular fibrillation and Danielopolu (33) has reported three cases in which auricular fibrillation followed the administration of the drug, in each instance the onset of fibrillation occurring coincidently with the maximum digitalis action. Danielopolu considered that in his cases the auricles were predisposed to fibrillation which was provoked by the stimulating effect of the drug on the vagus. Mackenzie (107) has reported a case in which auricular fibrillation set in at the time when an amount of digitalis sufficient to cause maximal effects had been given, and disappeared four days after the discontinuance of the drug. Robinson (126) studied a case of paroxysmal auricular fibrillation to whom digitalis was administered, but was unable to draw any definite conclusion

as to the influence of the drug on the persistence of the fibrillation. Agassiz (2) administered strophanthin intravenously to such a case, with the result of apparently prolonging the paroxysm of auricular fibrillation, although the ventricular rate was slowed by the drug. It is these cases of transient auricular fibrillation in which the question of the relation of the drug to the production of this cardiac disturbance is especially important. The evidence seems sufficient, as Fulton (56) points out, to warrant the conclusion that digitalis does predispose the auricles to fibrillation, and its use may therefore be disadvantageous in cases where it is desirable to prevent recurrent attacks of fibrillation, or where a cessation of fibrillation may be expected, although the drug may be very useful when fibrillation is present. Clinical judgment can be the only guide under such conditions.

Auricular standstill has been observed by White (157) as an effect of digitalis in cases of heart disease. In these cases, both electrocardiograms and graphic records from the jugular vein failed to show any evidence of auricular activity during the height of digitalis action. In all three cases, the auricular activity returned when the effects of the drug passed off. White considers this phenomenon as a rare result of digitalis administration, and no other similar cases are to be found in the literature. Atropin was administered in one case, but had no effect upon the cardiac mechanism except for a slight increase of rate.

White and Sattler (160) have also described a curious arrhythmia consisting of blocked auricular premature beats occurring in a healthy subject after 3 grams of digitalis had been taken. *Sinus arrhythmia* in which the rhythm of impulse formation is disturbed, is commonly observed with large doses of digitalis, as first pointed out by Wenckebach (155). A number of cases of *sino-auricular block* produced by digitalis have also been observed by the electrocardiographic method, as a result of digitalis action.

Pulsus alternans, a condition in which the regularly beating ventricles contract with alternating force, is generally considered a sign of disturbed contractility of the heart muscle, and of serious prognostic significance. Mackenzie (107) and Windle (162) each state that they have observed this phenomenon as a sequel of digitalis administration in two cases. Bastedo (5) reports one case

which he considered as possibly pulsus alternans produced by digitalis, but his records do not allow him to make a definite diagnosis, and his published curves are not characteristic of this condition. These cases are important as an indication that digitalis may affect the heart muscle, presumably directly, in such a way as to lower its efficiency. Bastedo believes that pulsus alternans results from a constriction of the coronary arteries produced by digitalis, but this idea must be considered purely hypothetical, as there are no definite facts to support it.

Weil (154) has brought forward a criterion for the early recognition of digitalis intoxication which is somewhat different from those that have already been mentioned. He has shown that, under the influence of the drug, the heart becomes more responsive to pressure over the vagus nerves in the neck, and he believes that a well marked vagus response during digitalis administration in a heart which was previously less responsive may be used as indicating the onset of toxic digitalis effects.

3. Fatalities resulting from digitalis bodies

It is not within the scope of this review to discuss fatalities resulting from amounts of digitalis far in excess of those used for therapeutic purposes. According to Sollmann (143) 2.5 grams of digitalis have proved fatal when taken at one dose, while 4 grams have been followed by recovery. Sollmann states that the symptoms of a fatal dose are those of "cumulation"—gastro-intestinal disturbances, slow and arrhythmic pulse, etc., lassitude, muscular weakness and sensory derangement. Death generally occurs suddenly, with dyspneic convulsions. Consciousness persists late.

Sudden death has been seen occasionally following the administration of the drug in the treatment of heart disease, and fatalities occurring under these conditions must be considered as possibly caused by the drug. During the administration of digitalis by mouth in the usual doses, it is difficult to say what rôle the drug might play as a cause of sudden death. Since the introduction of the intravenous method of administration, however, fatalities have apparently resulted from the injection of the digitalis bodies into a vein. These have most often followed the use of strophanthin, and according to inquiries made by

the writer, have been seen more often than the literature would make one believe. Bastedo (5) remarks that he has heard of one death following the intravenous injection of digitalis and of several such fatalities occurring in from three minutes to an hour after the injection of strophanthin. The writer has observed 1 case in which death occurred suddenly about five minutes after 1 mgm. of strophanthin was given intravenously, and at least 3 other such cases have been related to him by others. Recently Rahn (123a) has reported 2 fatalities following intravenous injections of strophanthin and has reviewed 16 other cases collected from the literature in which death occurred in such close connection with the intravenous injection of the drug as to make a relation of cause and effect seem very likely. In 11 of the cases the causal relation seems certain. Rahn discusses the clinical significance of these deaths and is of the opinion that some of these could have been avoided by smaller doses, longer intervals between doses and a better knowledge of previous administration of digitalis. He believes that the drug should be given by this method only after careful study of the patient. The sudden fatal termination and the relatively short interval between the injection and death seen in a number of these cases leads to the conclusion that strophanthin caused the ventricles to fibrillate, a cardiac state incompatible with life. Ventricular fibrillation is the final stage of cardiac intoxication in most cases when the digitalis bodies are injected intravenously into cats, as shown by Robinson and Wilson (134) and by Levine (92). It is likely that the fatal cases under discussion occurred in patients in whom cardiac damage had already rendered the ventricles prone to fibrillation.

Garrey (57) has investigated the underlying factors responsible for fibrillation of the cardiac muscle, and has advanced an explanation of this phenomenon on the basis of his experiments. The essential points in Garrey's conception of fibrillation are these. Fibrillary contractions of the heart muscle depend upon the establishment within the musculature of multiple regions of block or impaired conductivity. The impulses thus blocked or delayed take abnormal or circuitous paths, and return to the same portion of the muscle after the refractory state has passed off, but while other portions are still refractory. The latter portions are subsequently involved in a

similar manner, and the whole tissue mass is then thrown into a continuous incoördinated contraction, which is not initiated or sustained by new impulses arising from any definite location.

With these points in mind it seems reasonable to consider evidence of impaired conduction within the ventricles as a contraindication to the intravenous use of full doses of strophanthin or other digitalis bodies. Such evidence is sometimes obtained by the study of electrocardiograms, as certain abnormalities in the form of the ventricular complexes indicate delay or abnormal conduction routes in the ventricles. The bearing of these abnormal complexes to the administration of strophanthin has been discussed by Robinson and Bredeck (131), who express the opinion that such electrocardiographic findings should be taken as a contraindication to the intravenous use of strophanthin, and they show the relation these abnormal electrocardiograms may have to ventricular fibrillation.

Although the danger entailed in the intravenous administration of strophanthin has been generally recognized, other digitalis bodies have not received as much consideration from this point of view. Levine and Cunningham (94) however have studied the so-called margin of safety of intravenous digitalis administration in cats, and draw certain conclusions from their experiments bearing on the intravenous use of the drug. They determined the percentage of the lethal dose which produced the earliest demonstrable toxic signs. The minimal toxic dose was calculated in their experiments as the smallest dose that is required to produce ventricular extrasystoles, demonstrable by electrocardiograms. The margin of safety was taken as the difference between the minimal lethal dose and the minimal toxic dose. They have introduced

> the concept of the margin of safety of digitalis preparations because, in the practical use of the drug, the therapeutic dose is very close to the toxic dose. Therefore, it is of great importance to know how far removed the lethal dose is from the toxic dose, and whether the margin is greater in some preparations than in others.

They used aqueous extracts of several different samples of leaves, several different tinctures, and ampoules of Digifoline, Digalen and Digipuratum. They found considerable variations in different

animals both in susceptibility to the drug and in the margin of safety which varied from 27 to 64 per cent. The average margin of safety, however (the difference between the percentage causing death and that causing earliest evidence of toxicity), was 48 per cent of the lethal dose. This difference is identical with the results which Levine (92) obtained in previous work with crystalline strophanthin or ouabain. Levine and Cunningham (94) state on the basis of their findings that

> the practical consideration that follows from these experiments is that although the various digitalis bodies, when given by mouth, are generally regarded as much safer than intravenous administration of strophanthin, when the entire digitalis glucosides (either the aqueous or the alcoholic extracts) are given intravenously, the same risk is encountered as in using strophantin.

They found also but little difference in the rapidity with which the various digitalis bodies and crystalline strophanthin act on the heart when introduced directly into the circulation.

If these experiments can be applied to man, and it seems only safe to assume that they can, it must be borne in mind that the risk of introducing digitalis directly into a vein appears to be as great as when strophanthin is used.

The question of the percentage of the lethal dose which is employed in the treatment of heart disease has been discussed by Robinson and Wilson (134) in the light of their experiments in which the tincture of digitalis was administered intravenously to cats. They consider the inversion of the T wave of the electrocardiogram the digitalis effect offering the most useful comparison of the effects of the drug on the cat's heart and the effects obtained in man. The T wave became inverted in their experiments when from 20 to 30 per cent of the lethal dose had been injected. The maximum therapeutic effects of digitalis usually occur with a dose not much in excess of the amount sufficient to cause inversion of the T wave. Robinson and Wilson, taking these facts into consideration, have expressed as their opinion that the maximum therapeutic effects are probably produced in man by the administration of from 30 to 40 per cent at most of the lethal dose of the drug.

VIII. THE THERAPEUTIC EFFECTS OF DIGITALIS

The beneficial effects exerted by the digitalis bodies upon patients suffering from heart disease are dependent, not upon a single mode of action of the drug on a single organ, but upon a combination of effects. The relative importance of the various activities of digitalis in its therapeutic use has been the subject of much controversy for many years, and although much of this controversy has been cleared up, several points remain about which there is no unanimity of opinion. As has been stated, animal experimentation has added confusion, in some respects, to the problem of determining how digitalis benefits patients with heart disease, and the question can receive its final answer only by the study of patients.

The various effects which may enter into the therapeutic action of digitalis will be discussed separately and their relative importance will be considered in connection with the use of the drug in various forms of heart disease.

1. The effects on the heart muscle

a. The effect on ventricular contraction. The relation of the effect of digitalis on ventricular contractions to its beneficial influence in heart disease has been much discussed, but this problem has not yet been definitely solved. Its solution is difficult, partly because there has been no certain means of measuring the direct influence of the drug on the efficiency of the heart muscle, and partly because the various factors entering into the therapeutic action of the drug cannot be sharply differentiated from one another. In spite of the uncertainty which actually exists, digitalis has been generally considered for many years as a so-called "heart tonic," and its beneficial effect has been considered as mainly due to an increased output of the heart by its action on the muscle itself.

The older conception is well illustrated by a statement made by Balfour in his clinical lectures on Disease of the Heart, quoted by Schmoll (141).

> All the benefits we obtain from digitalis are inseparably connected with its tonic action; they flow from the power that digitalis has of increasing muscular activity, and the improved metabolism of all the tissues, but especially of the myocardium.

Schmoll expresses his belief that the drug acts as a specific by its effect on the tonicity of the heart muscle.

Schmiedeberg (140) basing his opinion apparently on the results of animal experiments states in the seventh edition of his text book, that the therapeutic action of digitalis is due almost exclusively to its effect on the heart muscle. He considers an increase in the elasticity of the heart muscle the most important effect of the drug and that the change in elasticity is also responsible for the systolic standstill of the heart produced by the drug. Schmiedeberg believes that all other effects of digitalis are mainly secondary to the increased force of the cardiac contractions which the drug calls forth.

Other students of the effects of digitalis on animals, notably Cushny, have found that the drug causes an increase in the output of the mammalian heart under experimental conditions, which occurs in excess of that which results from the slowing of the heart rate alone.

Another experimental pharmacologist Gottlieb (59) states that the work of a single contraction of the isolated mammalian heart may increase under the influence of digitalis two and a half to three times, and Gottlieb summarizes his conception of the therapeutic action of digitalis as due principally to more complete contraction of the ventricles and re-distribution of the blood in the vessels. He believes the drug may strengthen the contractions of the "weakened heart."

It does not seem profitable to enter into a discussion of the experimental studies of this subject, as the conditions under which facts have been adduced are not applicable to a consideration of the therapeutic action of digitalis. In this connection, Cohn (20) has said

> Those effects reported earlier, of changes in the magnitude of ventricular contractions gained in experiments, are more recently admitted (Joseph) to have been obtained by doses far too great. The much smaller doses now used are still much larger than are permitted in therapeutics, but even these fail to show marked changes in the extent of the excursion of the ventricular wall which was formerly held to indicate the nature of effective digitalization. The methods employed in pharmacology are not superior to those now available in clinical medicine. Both are on a par in respect to obtaining objective records of this phase of digitalis action.

In the absence of accurate means of measuring the therapeutic action on the heart muscle, the opinion of various clinical investigators must be considered more as impressions than as well founded convictions. In Mackenzie's (106) first studies on digitalis, he says that the good effect on the cardiac contractions may be due to the slowing of the cardiac rate, but under certain circumstances, the fact that digitalis may effect the function of contractability directly can be demonstrated in a most striking and convincing manner. In his later clinical studies, however, when he was in possession of a more extensive knowledge of the cardiac mechanism and its derangements, he stated that he was unable to determine that the drug affected the heart muscle, but admits that changes may take place in the heart which we cannot detect.

Wenckebach (155) believes that digitalis increases the strength of the human heart by its direct action on the heart muscle, but that there is no evidence that the drug acts on the obscure property, tone of the muscle. Edens (37) has advanced the hypothesis that the poor nutritional condition of the myocardium which is presumably present in heart disease tends to prevent digitalis from exerting its effort on the cardiac contractions, and offers this explanation for his inability to observe any direct action on the heart muscle. Cohn (20) in speaking of the effects of the drug when administered to patients in doses calculated to produce the optimum effects in heart disease stated in 1915, "that if digitalis increases the ability of the ventricles to pump blood, it does so by means of a change which is more subtle than can be distinguished by our methods."

With this limitation of the knowledge regarding this important factor in explaining the action of digitalis in mind, Cohn and Levy (26) have undertaken an investigation of the effect of therapeutic doses of digitalis on the contraction of heart muscle by means of animal experiments. They have been careful to use doses of the drug which were comparable in percentage of the lethal dose to those administered to patients. The tincture of digitalis and g-strophanthin were injected intravenously into dogs and cats, and alterations in volume output were studied in curves obtained by the use of the Roy and Adami myocardiograph.

The curves represent longitudinal linear alterations in the form of ventricles, and may, under the condition of cardiac contraction, represent changes in volume of the cavities and consequently of volume output. The results are reported as changes in the degree of contraction.

In 30 dogs, they obtained increased contractions 24 times; while other phenomena of digitalization revealed by electrocardiograms were less constantly observed. In 14 cats the degree of contraction increased 4 times, decreased 6 times and was unchanged 4 times, with even more frequent effects on electrocardiograms than in dogs. The effect on contraction differed, therefore, in cats and dogs. Blood pressure readings were also made in some of the experiments in which ether was administered and the chest opened. In order to rule out the effect of these procedures, several experiments were performed on unetherized dogs without operative procedures, the blood pressure being obtained from the carotid artery which had been previously freed from the tissues of the neck (van Leersum's method). In these experiments the electrocardiographic and blood pressure changes were similar to those of the dogs on which operations were performed. From these experiments, the conclusions are drawn that digitalis and strophanthin with doses of therapeutic range increase the contractile power of the cardiac muscle, and by so doing, increase the volume output. This result supplies a firm basis for the statement that these drugs may exercise a beneficial action on the normally beating heart by their action directly on the cardiac muscle. Their results regarding blood pressure and electrocardiography will be mentioned when these phases of the digitalis problem are considered.

b. The effect on the electrocardiogram. The effect of digitalis on the T wave of the human electrocardiogram has furnished evidence of a different kind from that which has been discussed, and it has served as apparently clear proof that the drug acts directly on the heart muscle when administered in therapeutic doses. Although no direct relation has been established between the change in the T wave and the efficiency of the cardiac action, the discovery of this effect has been very useful in studying digitalis and has marked a definite advance in our knowledge.

Cohn and Fraser (22) first reported briefly in 1913 that they had "found that as the result of digitalis intoxication, the T wave in the electrocardiogram often becomes negative or diphasic, but returns to normal after the effect of the drug has passed off. It is an interesting fact that, although atropin may cause rate and conduction to return to normal, this change in the electrocardiogram persists."

The influence of digitalis on the T wave of the electrocardiogram was studied in a series of patients by Cohn, Fraser and Jamieson (23) who made the first comprehensive report on this subject, although a number of scattered observations on animals and man had been previously reported by others. Cohn and his coworkers found that an alteration of the T wave occurred in 30 of 34 patients to whom full doses of digitalis were given, and that this alteration was generally observed before alterations in rhythm or conduction time had occurred or before gastro-intestinal symptoms disturbed the patients. For the most part, the changes in the T wave consisted, first, in a diminution in the height of the wave, and finally in an inversion. In cases yielding downwardly directed T waves before treatment, digitalis produced eventually upwardly directed waves and other variations in the T waves occurred. This portion of the electrocardiogram was affected in patients with auricular fibrillation and flutter, and in one patient with complete auriculo-ventricular dissociation, as well as in those with normally beating hearts. It is pointed out that the sign attains greater importance on account of its appearance early after the beginning of the administration of the drug. Changes in the T wave were detected after an equivalent of 1.2 grams or even less of the dried leaves of digitalis had been given.

The influence of atropin on the altered T wave was repeatedly tested, and full doses of the drug intensified the changes in the T wave during its transient action. Atropin alone, however, produced no changes in the T wave. The altered T wave persisted for some days after digitalis was discontinued, resembling, in this respect, other effects of the drug.

In discussing their results, Cohn, Fraser and Jamieson bring forward convincing arguments to prove that the alteration of the T wave is caused by the action of digitalis on the heart muscle. The effect that atropin has on the phenomenon indicate, however, that

the cardiac inhibitors, the vagus nerves, are capable of exerting an influence upon it. The effect of full doses of digitalis on the T wave of the electrocardiogram of healthy children was studied by McCulloch and Rupe (112). They found that the drug did not produce the same effects as readily or as frequently as in adults as shown by the observations of Cohn, Fraser and Jamieson, although larger amounts of the drug per unit of body weight were given to the children, and other evidence of digitalis action was abundant.

Since the appearance of the paper by Cohn and his coworkers, their results have been abundantly confirmed, both for man and animals. Robinson and Wilson (134) found the inversion of the T wave was the first constant sign of digitalis action to be detected by electrocardiograms when the drug was injected intravenously into cats. It occurred in their series when approximately 25 per cent of the minimum lethal dose had been injected, and the dosage necessary for its production was not altered when the vagi were cut.

Cohn and Levy (25) have recently compared the effects on patients of g-strophanthin given intravenously with the effects of comparable doses of digitalis (digipuratum) given by mouth. Only a preliminary report has been published. They studied the relative effect of the two drugs on the T wave of the electrocardiogram and found that strophanthin had little or no influence on the form of the T wave, which at most underwent only transient changes, while the usual effects were produced by digitalis.

c. The effect on the size of the ventricles. Several attempts have been made to determine whether the administration of digitalis leads to the development of *hypertrophy of the ventricles*. Cloetta (18) found that the continuous subcutaneous administration of digitalis to young rabbits had absolutely no effect upon the size of their hearts, as compared with a series of controls. Of a series of animals in which aortic insufficiency was artificially produced, those treated with digitalis showed less cardiac enlargement than those that were not treated.

Caro (12), on the other hand, noted cardiac hypertrophy in animals to which digitalis had been given over a long period of time as did Reinike (125) who compared the cardiac muscle with the skeletal muscles. The latter muscles did not participate in the hypertrophy

observed in the heart. This work is based on a very small number of animals (four rabbits and two dogs) and so the conclusions drawn can hardly be considered as justified. Gelbart (58) repeated Cloetta's experiments with rabbits in which aortic insufficiency was artificially produced, and found that four weeks after the valve damage, cardiac hypertrophy had developed which was, in no way, influenced by digitalis. In view of the conflicting evidence, the relation of digitalis to cardiac hypertrophy must be considered as an open question.

The influence of digitalis on *cardiac dilatation* presents an important question. Although ventricular dilatation may be favorably effected by the administration of the drug it is impossible to say whether this result is brought about by direct action on the heart muscle or whether it is secondary to other beneficial effects.

d. Chemical aspects of digitalis action. The action of digitalis on the cardiac muscle has been studied from *the chemical view-point* by Burridge (8), who made some pioneer contributions which may bring results of fundamental importance to the therapeutic use of digitalis in the future. He has concerned himself especially with the interaction of digitalis and calcium on the perfused heart. He studied changes in the degree of cardiac contractions resulting from changes in the calcium content of the perfusion fluid. During some observations on the cardiac reserve, he found that calcium determines the amplitude or the percentage of the contractile material possessed by the heart which is used up with each spontaneous beat. And further that, under certain conditions, digitalis is a drug which enables a given tension of calcium in the perfusion fluid to evoke the activity of a greater proportion of the whole contractile material than is the case in its absence.

Burridge (9), in a second paper, discusses some factors of the cardiac mechanism illustrated by reference to certain actions of barium and digitalis. He interprets his experiments to mean that digitalis renders the heart more susceptible to calcium, as a given amount of calcium had more effect on the heart after treatment with digitalis than before. Crystalline digitoxin was used. He studied (*a*) the effect of digitalis on changes in the amplitude of contractions with fixed amounts of calcium, and with amounts of calcium necessary to evoke a fixed proportion of the whole contractile material;

(*b*) on the amount of tonus produced by a given amount of calcium and vice versa; and (*c*) on the amount of shortening of the refractory period produced by a given amount of calcium. Not only was calcium more effective but less calcium was required to produce constant effects after the heart had been exposed to digitalis. The response of the heart to calcium could be increased five to tenfold by treating it with digitalis, the effects of which persisted after the drug was withdrawn. The amount of calcium necessary to allow normal contractions may produce systolic standstill of a digitalized heart. A difference was noted in this respect, however, in hearts that had been long perfused and in fresh hearts, digitalis causing more marked effects in the latter.

Burridge believes that digitalis may be considered as a cardiac "lubricant," and should be classed with the secretions of the adrenals and pituitary gland in this regard.

Loewi (104) has also studied the relation of the effects of calcium and digitalis. He is of the opinion that in cases of heart disease the capacity of the heart for stimulation by the physiological calcium content of the blood is depressed. Strophanthin, Loewi believes, brings the sensitiveness of the heart to calcium back to normal.

These studies on the perfused heart represent conditions so far removed from those obtained in the treatment of heart disease that direct application is unwarranted. On the other hand, the work of Burridge and Loewi is very interesting and should not be lost sight of in attempts to find the fundamental principles underlying the action of digitalis on the human heart.

Levine (92) has discussed the question of whether the action of the digitalis bodies on the heart is a physical or a chemical process. His review of the work bearing on this question shows how difficult it is to find its answer. Certain facts indicate that probably chemical changes and physical action each play a part. The general condition of the heart, the temperature, rate and pressure of the perfusion system, and its organic and inorganic constituents are all factors difficult to resolve. Levine's perfusion experiments with strophanthin-g have led him to believe that the heart utilizes only a small portion (in the neighborhood of 10 per cent) of the drug to which it is exposed, regardless of the concentration at which it reaches the heart.

A toxic effect results when the heart has taken up a certain total of the drug, which is a definite small fraction of its own weight. If this theory be correct, it explains why, in concentrated solutions, the total amount is not important, for the small part that is taken out by the heart does not appreciably alter the concentration, while when very dilute solutions or small quantities are used, the amount taken up by the heart diminishes the remaining concentration appreciably; that is, the "digitalis pressure" becomes lessened. In these experiments, the rapid injections forced an adequate amount of strophanthin into the heart rapidly, and produced the toxic effect; in the slow injections, the same total amount of the drug was taken up by the heart, only more slowly.

2. The effects on the cardio-inhibitory mechanism.

Since the demonstration by the Weber brothers of the cardio-inhibitory mechanism, much interest has been shown in its relation to the action of drugs affecting the heart, and pharmacologists have had to take into account the possibility of indirect action of drugs on the heart through its nervous mechanism. The illuminating analysis of the cardiac action of the vagi by Engelmann has been of much value in attempts to understand the action of drugs affecting the heart. He showed that the heart possessed the properties of contractility, conductivity, rhythmicity and irritability, and that all these properties were depressed when the vagus nerves were stimulated. This conception has not only done much to form a basis for the explanation of abnormalities of the heart beat, but it has also been useful in understanding the effects that digitalis exerts on the heart.

a. Vagus stimulation. Traube was the first experimenter to find that cutting the vagus nerves altered the effect of digitalis on the heart. His later studies led him to conclude that digitalis stimulated the cardio-inhibitory centre in the medulla, and affected the heart through the vagi. Ackermann, according to Boehm (6) demonstrated in 1871 that digitalis failed to slow the heart of animals after atropin had been injected. Boehm, who was also one of the earliest experimenters with digitalis, concluded from his work with frogs, that the drug heightened the irritability of an inhibitory centre in the heart, and thus increased the susceptibility of the heart to vagus action.

Cushny (29) made an important contribution to the action of digitalis by his studies on the mammalian heart. He showed that the drug acted both by direct action on the muscle and by stimulation of the cardio-inhibitory centre. He divided its action into the inhibitory and the muscular stages, and concluded that the beneficial stage of its effect in heart disease resulted from its action on the heart muscle, while its inhibitory action was undesirable from the therapeutic standpoint. The fact that digitalis has two modes of action on the heart has made it difficult to reach definite conclusions as to their relative importance, and to give a clear conception of its effects.

Although the vagus effects of digitalis have been considered by most students of the subject to result entirely from the direct stimulation the cardio-inhibitory centre, other opinions have been held. Schmiedeberg (140) considers that vagus stimulation is secondary to the increased blood flow produced by the action of digitalis on the heart muscle. Kockmann (89) concluded from his experiments on dogs that digitalis causes slowing of the heart at least in part by stimulation of the peripheral end of the vagi. He obtained cardiac slowing in dogs by intravenous injections of various digitalis bodies after the vagi had been cut and found that this slowing was replaced by acceleration when atropin was given. Etienne (50) repeated these experiments and was unable to confirm Kockmann's observations.

Green and Peeler (60) studied the action of digitalis on the cardio-inhibitory centre when perfused through the isolated head and brain of the turtle. In their experiments, the head was completely isolated from the general circulation, and all tissues in the neck region except the vagus nerves were severed; the connection through the nerves being the only one maintained between the head and the body. The cardiac movements were recorded by a direct attachment of the ventricular apex to the recording lever. They found that when digitalis was perfused through the turtle's brain, the cardio-inhibitory centre was strongly stimulated and that not only was the rhythm of the heart inhibited, but the conduction of the cardiac impulses was also depressed. The weight of evidence is strongly in favor, therefore, of the conception that the vagus effects of digitalis on the heart are mainly or entirely the result of the direct stimulation of the cardio-inhibitory centre, although other factors may take some minor part in their production.

b. The effect on cardiac rate. The two chief cardiac effects of digitalis stimulation of the vagus centre are slowing of cardiac rate and depression of conduction of the cardiac impulse from auricles to ventricles. The other cardiac effects of vagus activity, inhibition of contractility and of irritability may be masked or overcome by the effect of the drug directly on the heart muscle, for they are not observed.

Reduction of the rate of the heart beat was the first digitalis effect to attract attention in experiments on animals, and these observations profoundly influenced the conceptions regarding the therapeutic use of the drug. Digitalis has been used by physicians for many years with the expectation of slowing the heart rate of patients in the same manner in which slowing is produced in animals. It is true that the reduction of the accelerated cardiac rate is without doubt the most important effect of digitalis in heart disease but this valuable effect occurs in a striking manner only in one form of cardiac disturbance, namely, auricular fibrillation, in which digitalis accomplishes the reduction of cardiac rate by an action quite different from that causing the slowing observed in animals and in man with normally beating hearts. This point will be discussed later when the use of the drug in auricular fibrillation is considered, but to avoid confusion, it is necessary to draw the distinction at this time between the action of digitalis on the normally beating heart and on the heart in which the auricles are in a state of fibrillation. It is only when these two conditions are differentiated that reliance can be placed on statements regarding the influence of the therapeutic action of digitalis on the cardiac rate. As it was not possible to determine with certainty the existence of auricular fibrillation before the employment of the electrocardiograph, only the literature of approximately the last ten years can be said to furnish reliable evidence on this point.

The question under discussion here is the ability of digitalis to slow the normally beating human heart by inhibition through the vagi of the rate of impulse formation.

Divergent opinions have been expressed by various students of digitalis. Wenckebach (155) states that the regularly beating heart is slowed by the action of digitalis on the vagus nerves and compared its action to the effect obtained by stimulation of the vagi by pressure

over their trunks in the neck. On the other hand, the drug was found to have almost no effect in most cases with normal rhythm in the series carefully studied by Mackenzie (107). He observed occasionally, however, striking slowing of the cardiac rate in cases with normal rhythm following the administration of digitalis, which he thinks is possibly due to the stimulation of the vagus nerves by the drug. Cushny (29) observed slowing of the heart in 6 of 18 patients with normally beating hearts to whom full doses of digitalis were given. The relation of the slowing in such cases in which it does occur to vagus action was studied later by Cushny, Marris and Silverberg (32). They noted the effect of vagus paralysis by atropin in patients affected by digitalis, and attempted to distinguish between the effects of the drug directly on the heart muscle and those induced through vagus stimulation. They concluded that the effects produced through the vagi do not play any part in the beneficial action of the drug.

Cohn and Fraser (22) have reported repeated observations on the effect of digitalis on twelve patients with normally beating hearts. Daily electrocardiograms were taken and the drug was administered until a disturbance in the rhythm of the heart was effected, at which time the patients usually had gastric symptoms. In regard to the effect of digitalis on the heart rate they say:

> Slowing of the heart, even when the rhythm is normal, is still taken in many quarters as a measure of the efficiency of digitalis. The slowing of the heart which takes place *after* the onset of the symptoms of intoxication can hardly be taken to be of benefit. But before the symptoms occurred, slowing took place in only one patient, and this one was the subject of abrupt fluctuations in rate without the use of drugs. Slowing was observed in five more patients, but not until two days after rather severe symptoms of intoxication had set in. Two of these patients had quite normal hearts, anatomically and functionally. It appears then that if the patients are divided into two groups, those in whom slowing occurs before and those in whom it occurs after the onset of digitalis intoxication, slowing will rarely be observed in the first group—and the slowing which is observed in the second group is an effect which can, in the long run, scarcely be desirable.

In a later publication, Cohn (20) states:

We have been led to conclude from our observations that digitalis slows the sinus rhythm only in the group of hypodynamic hearts, and that to produce slowing is not a primary function of digitalis in therapeutic doses.

White and Sattler (160) report the effects of large doses of digitalis on ten healthy young adults. The effects of the drug were observed by daily electrocardiograms. Marked slowing occurred in two subjects, the heart rate reaching 43 beats per minute in each instance. In two other subjects, the heart rate became lower than usual at night when under the influence of the drug. In the other six cases, no change in heart rate occurred.

Parkinson (119) administered digitalis in full doses to 20 soldiers with cardiac symptoms, a rapid pulse rate and with normally beating hearts. (Effort syndrome.) He reports that the heart rate was reduced but little, and that the group of patients was scarcely influenced by digitalis. Pratt (122) states that his experience with digitalis confirms the findings of Mackenzie and Cohn and Fraser that digitalis rarely slows the rate of normally beating hearts until toxic symptoms are produced.

Robinson (130) has reported the effects of large single doses of digitalis on a series of approximately one hundred patients, and although striking effects were obtained in cases with auricular fibrillation, practically no change in the heart rate was observed in patients with normally beating hearts to whom the same amounts of digitalis were given.

On the other hand Sutherland (147) reports slowing of the normally beating heart by digitalis. He treated a series of cases of rheumatic heart disease with rapid cardiac rates, usually in children or in young patients. He states that digitalis caused slowing of the cardiac rate practically uniformly and the results in these cases were as definitely good as those usually seen in cases of auricular fibrillation.

McCulloch and Rupe (112a) have quite recently confirmed Sutherland's observations. They studied the effects of the drug on a series of children with heart disease, and found that slowing of the heart-rate of ten or more beats occurred so constantly when full therapeutic doses were given, that this effect could be used as a sign of digitalis action. They recommend the use of the drug in children with heart disease for the purpose of slowing the heart rate when it is more or less

persistently accelerated, and when such causes of acceleration as pain, fatigue, excitement and fever have been removed.

Pardee (118a) has also observed slowing of the normally beating heart following the administration of large single doses of the tincture. The onset of the slowing in the nine cases studied was noted to occur before the changes in the T wave of the electrocardiogram in three patients. The two effects occurred synchronously in four patients, while the T wave changes occurred first in two. The heart was considered as slowed when the rate was found to be ten beats per minute slower after the drug was given than in several counts before. The size of the single doses was determined by giving 1 minim of a fairly good tincture per pound of body weight.

Certain facts that have been demonstrated by animal experiments seem to show why the reduction of the cardiac rate is not more often seen in patients. Halsey (63) found that the dose which causes slowing and other signs of vagus stimulation lay between 30 and 40 per cent of the minimum lethal dose of g-strophanthin, of digipuratum and of a fluid extract of digitalis given intravenously in dilute solutions in about fifteen minutes. Robinson and Wilson (134) slowly administered a diluted tincture of digitalis intravenously into a series of cats and followed the effects of the drug by electrocardiograms. In these experiments, the heart rate was slowed gradually, the effect being first seen with about 25 per cent of the minimum lethal dose, while the maximum slowing occurred when about 70 per cent of the minimum lethal dose had been given. In a second series of cats in which the vagi had been cut, practically no slowing of the heart rate was observed.

It seems evident that the amount of digitalis which is necessary to stimulate the cardio-inhibitory centre sufficiently to cause slowing of the heart-beat is usually greater than the amount that can be given to patients without the production of toxic symptoms. However, individuals whose vagus centres are more easily stimulated than usual or whose hearts are unusually susceptible to the slowing action of the vagi, are exceptions to this rule. Children apparently fall into this category. It is evident that the reduction of the rate of the normally beating heart should no longer be looked upon as an effect which digitalis should be expected to produce at least in adults although such an effect is desirable in many cases of heart disease.

c. The effect on conduction. The depression of the conduction of the cardiac impulse between the auricles and ventricles has already been discussed briefly as a toxic manifestation of digitalis. As this effect plays an important part in the therapeutic action of the drug, and as it is at least in part brought about through the cardio-inhibitory mechanism, it deserves further consideration at this point.

The experimental studies of von Tabora (148) drew attention to the fact that digitalis depresses conduction through its action on the cardio-inhibitory centre. He concluded that this effect is produced both through the vagi and by the direct action of the drug on the conducting pathway. He also showed that digitalis is more effectual in animals when the A-V bundle had been injured.

Although the clinical recognition of the influence of digitalis on conduction has been general since it was first pointed out in patients by Mackenzie (106) there has been a discussion as to whether it should be regarded mainly as an effect of vagus stimulation or as an effect produced by the direct action of the drug on the heart.

Although the general opinion seems to favor the idea that vagus stimulation is largely responsible for the effects of digitalis on conduction, Cushny, Marris and Silverberg (32) concluded from their study of this problem on patients that the cardio-inhibitory mechanism is of minor importance, and they emphasize the direct action of digitalis on the heart. Cushny (31) expresses the opinion in a later publication, however, that digitalis may effect conduction by either method, and the condition of the heart is the factor determining which of the two methods will predominate. He seems to believe that in normal hearts the conduction is depressed through the inhibitory mechanism; while in diseased hearts, where conduction is already damaged, heart-block or delayed conduction is caused by the direct action of the drug.

Wedd (152) who studied the effect of atropin after full doses of digitalis in a large series of cases, concludes that in all cases the action of digitalis is both central, in the medulla, and local, in the myocardium. He observed that in 100 per cent of his cases of auricular fibrillation, and in 76 per cent of those with normal mechanism, the heart rate failed to return after atropin injections, to the level at which it was before being slowed by digitalis. He believes that it is

possible to measure the local action of the drug by the degree which atropin fails to restore the heart to its original rate. Wedd considers that Cushny has perhaps gone too far in ignoring the action of digitalis on the cardio-inhibitory centre in certain types of heart disease, in which the local action on conduction seems to predominate.

The observations of Cohn and Fraser (22) show clearly the manner by which digitalis affects the conduction of normally beating hearts when presumably not extensively damaged by disease. The twelve patients to whom digitalis was given until symptoms of intoxication appeared, were studied by means of electrocardiograms. In all but one, conduction was affected by the drug, as evidenced by lengthened conduction time or by blocked auricular impulses. The administration of atropin by subcutaneous injections caused the conduction to return practically to its normal condition, in all cases, regardless of the degree of depression that had been present. It is evident therefore that in these cases the effect on conduction was entirely produced by stimulation of the cardio-inhibitory mechanism, as it was abolished with vagus paralysis. The interesting observation was also made that the rate of the heart when reduced was not restored by atropin in a manner that paralleled the restoration of conduction.

White and Sattler (160) confirmed these observations in ten healthy young adults. They found that atropin completely removed the effect of digitalis on auriculo-ventricular conduction, and they concluded that the effect on conduction was almost entirely, if not entirely due to increase of vagal tone and irritability.

The foregoing observations demonstrate that the conducting system is capable of being effected by digitalis when the heart is presumably normal. However, depression of conduction does not become marked until large doses are given. Cohn (20) has observed delayed conduction forty-eight hours after the administration of the drug was begun, and in many instances, the conduction time gradually lengthened during the succeeding three to five days until partial block occurred. Heart block may occur, however, with extreme abruptness within a few hours. In the healthy young subjects studied by White and Sattler (160) the first effects on conduction were seen after 1.5 to 1.8 grams of the leaf had been administered; but there was no marked prolongation of the conduction time until 2.7 grams had been

taken. This latter dose is about that which, on an average, produces toxic symptoms.

There is no doubt that in heart disease when the tissues of the conducting pathway are damaged, digitalis heart-block may be produced by much smaller doses of the drug than those producing it in normal hearts, but it can no longer be said that digitalis produces heart-block only in hearts in which the conducting mechanism is already damaged. The problem of the conduction effects of digitalis in heart disease is a complicated one, and considerable light is still needed on this subject for its complete understanding.

Depression of conduction may be an important factor in the beneficial effects of digitalis in two ways. In the first place, it prevents the improper stimulation of the ventricles by the auricles. As will be seen when auricular fibrillation is discussed, the ability of digitalis to prevent stimuli from reaching the ventricles is of paramount importance in the treatment of certain forms of heart disease. In the second place, depression of conduction allows a longer period to elapse between auricular and ventricular systole, and Cohn and Fraser (22) have suggested that this may be a matter of some importance in the treatment of patients who have mitral stenosis. They point out that in these patients,

> the initial and most important of the factors which tend to disturb the circulation is the narrow auriculo-ventricular orifice, which prevents the complete empyting of the left auricle within the time allowed before the ventricles contract. If one could lengthen the conduction time and could keep it lengthened, thus separating the contractions of the auricles and ventricles as widely as possible, much aid could be given patients of this class in maintaining a satisfactory circulation. There is reason to believe that this can be done.

3. The effects on the blood vessels

a. The effect on blood pressure. Cushny (28) states that Blake discovered in 1839 that digitalis caused an elevation of blood pressure in experimental animals. From that time until quite recently, this effect and the effect on the heart rate have almost predominated the field of digitalis action. It was generally believed that the arterial pressure was raised by increased force of the ventricular contractions

and by the constriction of the blood vessels. It is an interesting fact that neither of these effects has been demonstrated in man as a direct action of the drug, although there is indirect evidence that the first of these effects occurs, as was pointed out, when the action of digitalis on the heart muscle was considered. The effect of digitalis on the blood pressure is of such importance that it is desirable to consider briefly some of the experimental work bearing on this subject before reviewing the more recent clinical studies.

The chief exponents of the idea that digitalis has a direct action on the blood vessels have been Gottlieb and the members of his school. Numerous investigations have been reported from his laboratory bearing on this subject.

The most important study to lead to the belief that the digitalis bodies are capable of producing marked vascular constriction through direct action on the vessel walls has been, according to Eggleston (43) that of Gottlieb and Magnus, published in 1902. By the use of doses of various digitalis bodies which were five to fifteen times the minimum lethal dose, they produced striking elevation of blood pressure in experimental animals, which was in part caused by constriction of the splanchnic vessels by direct action of the drug upon their walls.

Among other publications from Gottlieb's laboratory which are of interest, several may be mentioned. Kasztan (87) in 1910 showed that when Ringer's solution containing not more than 0.05 mgm. of crystalline strophanthin to 100 cc. was perfused through the kidneys of dogs, cats and rabbits, arterial dilatation took place; while if the solution contained 0.1 mgm. of strophanthin, arterial constriction occurred. The weaker solution when perfused through the intestinal vessels, however, caused them to constrict. This work was confirmatory of that of Jonescu and Loewi (85), who considered that dilatation of the renal vessels occurred as a direct peripheral effect on the vessels. Fahrenkamp (51) repeated the work of Kasztan, using, however, digitoxin instead of strophanthin. He obtained an effect on the renal and intestinal vessels similar to that observed by Kasztan. He found further that concentrations of digitoxin which contracted the kidney and intestinal arteries had no effect on the vessels of the skin and muscles. Cats and rabbits were used, and Fahrenkamp found that 0.7 mgm. of digitoxin per 100 cc. Ringer's solution caused dilatation

of the renal vessels of the cat; that 0.48 mgm. produced the same effects in rabbits, and that 1.2 mgm. of digitoxin caused contraction of these vessels in both animals.

Later Joseph (86) investigated a similar subject in Gottlieb's laboratory and studied simultaneously the effect of small doses of strophanthin and digitalis (digipuratum) on the heart and on the vessels. He attempted to use doses comparable to those employed in the therapeutic use of these drugs; but, as a matter of fact, his doses appear to be considerably larger as a rule. He found that in rabbits and cats the action of these drugs on the heart and on the vessels are not synchronous and that they seem therefore to be independent. Digitalis was found to cause at first a dilatation and then a constriction of the vessels, which in the intestines, outlasted all other effects. The kidney vessels dilate while the intestinal vessels contract. Joseph considers that he succeeded in demonstrating vascular effects with any dose that affected the heart. The slowly developing and persistent narrowing of the intestinal vessels is the most frequent and most striking digitalis effect which he observed.

Gottlieb (59) has laid great stress on these and similar investigations. He holds the view that the power of digitalis to alter the size of important vascular systems is of prime importance, and that the alteration of the distribution of the blood which digitalis causes is the main factor in its curative action. He believes also that the vascular changes caused by digitalis are, in large measure, responsible for an elevation of the blood pressure in man when the drug is given in therapeutic doses.

Krehl (90) has also recently stated that he considered the best results from the use of digitalis were obtained in patients in which there is altered blood distribution.

Eggleston (43) has recently published a critical review of the investigations of the Gottlieb school and has commented upon their bearing on the question of *blood pressure* changes caused by digitalis in man. He points out especially the great divergence in dosage under the two conditions and says

> it must be quite obvious to anyone who gives the matter a moment's thought that it is utterly fallacious to reason from such experiments that similar effects would be produced in man from the therapeutic use of digitalis or its congeners.

The discovery that elevation of blood pressure is not a constant or conspicuous effect of digitalis in man occurred when the sphygmomanometer was introduced into clinical medicine, and when accurate objective observation began to replace deductions from animals and observations strongly influenced by preconceived ideas. In 1901 Sahli (quoted by Eggleston) stated that in cases with circulatory stasis and high blood pressure, digitalis not only relieved the stasis, but also very often reduced the blood pressure by from 30 to 40 mm. of mercury. The findings of Sahli have been amply confirmed by such careful students of the effects of digitalis on man as Mackenzie (108), Cushny (29) and Cohn (21). Eggleston (43) has summarized the findings of a number of observers[1] who have studied the effect of digitalis on blood pressure. He says:

> We find that the systolic blood pressure was recorded for 181 cases. In 66 of these, or about 36 per cent, the systolic pressure is stated to have risen or to have tended to rise; in 57 or 31 per cent, it fell; and in 58, or 32 per cent, it is recorded as having shown no change. In 116 instances in which the diastolic pressure is mentioned, it is stated to have been increased in 24, or 15 per cent; and to have fallen in 76 or 65 per cent. While the actual extent of the changes is not always stated, it would seem that digitalis is about as likely to influence the systolic pressure in one direction as in another, or not to alter it at all. With the diastolic pressure, however, the chances are nearly two to one that digitalis will cause some reduction, and the chances are more than three to one in favor of its reducing it as compared with the likelihood of its raising it. Other things being equal, this evidence certainly does not point to the occurrence of any marked vasoconstrictor action of the drug in man. The opinions expressed by the several authorities cited are in very general agreement that digitalis has little constant influence on the systolic blood-pressure when used therapeutically, and some even go so far as to suggest that it actually often causes some vasodilatation which would account for the reductions observed in the diastolic pressure.

Eggleston's own observations have been perhaps the most valuable contribution to the study of the influence of digitalis on blood pressure

[1] The work here summarized is that of Czyhlarz, Gross, Neu, Geisböck, Schwartz, Fellner, Szinnyei, Price, Lawrence and Cadbury. References to their papers are given by Eggleston.

in man. The various conditions of the study were carefully controlled. An assayed extract of digitalis or digitoxin in the form of tablet triturates or of the granules of Nativelle's digitaline crystalisée were given in large doses. The full amount calculated, according to body weight, was administered in twelve or eighteen hours and the effects of the drug on the heart were followed by polygraphic and electrocardiographic methods. The blood pressure was recorded for three days before and three days after the drug was given. Eggleston's series consist of 14 patients, 6 of whom had high initial pressure while 8 had normal or low initial pressure. His study revealed the fact that

> the administration of large doses of digitalis or digitoxin has very little tendency to elevate the systolic pressure, this having been increased by 11 mm. of mercury in one, and 15 mm. in a second case. In only one case was the systolic pressure materially reduced, namely by 23 mm. of mercury. On the other hand, the diastolic pressure was significantly lowered in 7, or 50 per cent of the cases, while it was never significantly raised.
>
> It is evident, therefore, that digitalis and digitoxin have very little influence on the systolic pressure in either direction, that they tend to produce a significant reduction in the diastolic and more decidedly, to produce a material increase in the pulse pressure.

Eggleston found that alteration in the pulse rate did not offer an explanation for the changes occurring in the diastolic pressure. The facts brought out by this study abundantly warrant the conclusion that "there is no evidence that either digitalis or digitoxin has any direct action on the vessels when given to man even in large therapeutic doses."

Eggleston's observations show that the net changes in the systolic, diastolic and pulse pressure differ in different cases in order best to meet the condition prevailing, and they indicate that studies on the blood pressure effects of digitalis must always take into strict account the condition of the patients under observation.

It will no doubt be some time before clinicians generally learn that arterial hypertension does not contraindicate the use of digitalis, but may in fact be advantageously affected by its action. However, clinicians have reported favorable results from the drug in cases with elevated blood pressure. Windle (162) has recently stated that

digitalis is valuable to patients with degenerated arteries, high blood pressure and anginal symptoms and may bring about an immunity from angina. Lawrence (91) has expressed similar views after a careful study of the blood pressure in 26 cases, during treatment with digitalis. Danielopolu (34) treated 36 cases of arterial hypertension with Nativelle's digitaline, although he remarks that the work dealing with the action of digitalis on the arteries made him hesitate to do so. His patients had arterial sclerosis and nephritis. Of the 36 patients a fall in the systolic pressure occurred in 19, while in 24 patients, the diastolic pressure was reduced: In 2 patients, a fall in systolic pressure alone was observed. The reduction of the arterial pressure amounted to 10, 20 or even 30 mm. of mercury.

During a study of one hundred patients, some of whom had hypertension, to whom very large single doses of the tincture of digitalis were given, Robinson (130) noted that the systolic pressure tended to approach more nearly the normal level after the drug was given. In other words, elevated blood pressure fell, while abnormally low pressure rose after the drug was given. These observations confirm Eggleston's more detailed study.

It is by no means desirable that the state of the blood pressure should be no longer taken into consideration in determining the indications for the use of digitalis or in studying its effects in man. Recent experimental observations by Cohn and Levy (26) indicate that under conditions kept as nearly similar as possible to those pertaining in the clinical use of digitalis, the blood pressure of dogs may be elevated by g-strophanthin and the tincture of digitalis. During a study of the effects of therapeutic doses of digitalis on the contraction of the heart muscle, they studied the blood pressure of normal dogs when not under operative conditions by the method of van Leersum, and noted the effect of the drugs used when given in doses on the same body weight basis as used in patients, which produced no evidence of severe intoxication. In the few animals thus studied, they found that the blood pressure usually rose, the increase varying from 20 to 66 mm. of mercury.

Cohn and Levy seem to attribute the rise of blood pressure which was transient, to the effect of the drugs on the contraction of the heart muscle.

It is not possible to dismiss the subject of the effect of digitalis on blood pressure as non-existing, but the older ideas must give place to those resting upon the accurate clinical studies that have been made since the introduction of the sphygmomanometer, and arterial hypertension must not be accepted as a reason *per se* for withholding digitalis when it is otherwise indicated.

b. The effect on the coronary circulation is a subject about which there has been a certain amount of speculation and which has also been studied experimentally. Although theoretically it is of much interest, practically, no facts have been established which bear directly on changes in the coronary arteries with therapeutic doses of the drug, and no definite information regarding the effect of digitalis on the coronary circulation of man has been obtained.

Eggleston (47) has recently reviewed this subject. He points out that it assumes some importance because of statements that appear in some recent textbooks to the effect that digitalis may cause a dangerous constriction of the coronaries, and is therefore contraindicated in angina pectoris. There seems to be no evidence for the idea that digitalis causes coronary constriction. The experiments of Felix Meyer and of Sakai and Saneyoshi (quoted by Eggleston) have shown that the coronaries do not contract under the influence of digitalis but if they are affected at all, they probably dilate. Bond (10) investigated the influence of digitalis and strophanthus on the coronary blood flow of dogs, measuring the coronary flow by the number of drops in a given interval of time coming from the coronary veins. He could find no effect attributable to these drugs, and concluded that the coronary blood flow is probably regulated by the systemic blood pressure, as it was decreased when the blood pressure was lowered by nitroglycerin and amyl nitrate.

Voegtlin and Macht (150a) investigated the action of a number of drugs of the digitalis group on strips of mammalian coronary arteries. They found that digitoxin, crystallized German digitalin of Merk and bufagin especially caused coronary constriction under the conditions of their experiments, while digitonin and preparations containing this saponin-like body caused relaxation. Strophanthin was found to be practically inert in this respect. Voegtlin and Macht think that these observations have considerable importance in the therapeutic use of

digitalis especially in the treatment of angina pectoris, when they believe a nitrite which they find causes coronary relaxation should be combined with the digitalis.

Eggleston (47) also discusses the relation of the blood supply to the heart muscle through the coronaries to pulsus alternans, and expresses the opinion that although this derangement of the heart may occur apparently as a result of digitalis, this is no reason for considering that digitalis brings on this derangement by coronary constriction. Pulsus alternans may also disappear when digitalis is given.

It is safe, therefore, to say that at present there is no reason to believe that the digitalis bodies affect the blood flow through the coronary arteries by direct action on these vessels.

c. The effect on the venous blood pressure in man has been studied by Capps and Matthews (11), who used both digitalis and strophanthin, and obtained no evidence of changes in the venous pressure.

4. The effects on the kidneys

The use of digitalis as a diuretic begins with its introduction into medical practice in 1785, as Withering (163) recommended it especially for the removal of dropsy and emphasized its action on the kidneys rather than its action on the heart. Withering mentions diuresis as one of the cardinal effects of digitalis, and recommends that its occurrence should be taken as an indication for discontinuing its administration.

The manner in which digitalis causes diuresis has been one of the controversial points regarding the action of the drug. The chief discussion has arisen over the question as to whether diuresis is in reality a direct effect of the drug on the kidney and its vessels, or whether it is secondary to an improved state of the general circulation. Various opinions are held regarding this point.

The experimental studies of Gottlieb and Magnus, Jonescu and Loewi (85), Kasztan (87), Fahrenkamp (51), and Joseph (86) have already been referred to in discussing the action of digitalis on the blood vessels. The fact that dilatation of the renal vessels is caused by weak solutions of the digitalis bodies cannot, as it was previously pointed out, be taken as evidence from which conclusions can be drawn regarding the effects of therapeutic doses of the drug in man.

The conditions are far from comparable. On the other hand, these experiments clearly indicate that the kidney vessels differ in their reaction to digitalis from other vessels, especially those of the splanchnic area. This fact is inviting as a basis upon which to build a theory of digitalis diuresis, as Gottlieb and others have done. Generally speaking, the ground is considered insecure, and the results of clinical studies show that the diuretic effects of digitalis do not occur as they would were the theory of Gottlieb correct. The quantitative study of diuresis has recently been much improved by the organization in hospitals of means of accurately measuring the intake and output of fluids of patients and accurate records of body weight.

Since the introduction of such methods, Mackenzie (108) has reported that diuresis is not very evident in patients even when digitalis is given to the stage of toxic symptoms, and he considers that no definite conclusions are justified regarding diuresis from his careful study of the action of digitalis. Cushny (29) observed diuresis only in patients in whom dropsy was present, and Agassiz (2) obtained similar results from the intravenous administration of rather small doses of strophanthin in cases of auricular fibrillation. Diuresis occurred only in the presence of edema. Cohn (20) has also emphasized this distinction, and reports that in the group of patients which he studied with much care, diuresis was never seen in patients without edema. He concludes from his experience that a specific effect on the urinary output does not occur as the result of giving digitalis to patients with normally beating hearts without the presence of edema. Cohn (21) has also found that diuresis is usually marked when edema is present. Christian (16) in emphasizing the beneficial effects which may be obtained from digitalis in chronic cardiac cases with edema in whom there was no irregularity of the pulse, points out the striking diuresis and loss of body weight which may occur in these patients, and publishes a series of charts illustrating his results. There seems to be in his cases a relation between the amount of edema and the extent of diuresis. The reports of other observers tend to confirm these findings. It is evident that some factors other than dilatation of the renal vessels take part in the increased flow of urine produced by digitalis. The question of the effect of digitalis on water exchange has been recently discussed

by Krehl (90) who is no doubt more or less influenced by the views of his colleague, Gottlieb.

The question of the action of digitalis on the kidneys has been investigated by Reinike (124) by an experimental method differing from those already mentioned. Digitalis was administered over a long period of time to rabbits, and was found to cause an enlargement of the kidneys as compared with those of control animals. This suggested that the kidneys had undergone excessive activity under the influence of the drug. No definite conclusions, however, are justified from Reinike's experiment, as the drug was given to only four animals, and they did not show uniform results.

In spite of the fact that there is nothing definite on which to base a claim that digitalis produces diuresis by direct action on the kidneys, the position that the kidneys play no part in digitalis diuresis does not seem to be entirely justified. However, several pharmacologists who have been especially interested in the action of the drug state that diuresis is entirely a secondary effect.

Hatcher (70) says:

> None of the drugs of this group are actively diuretic through any direct action on the kidneys. They induce diuresis solely through an improved circulation. That does not mean either a higher or a lower blood presure in every case; it means a more effective circulation, one better adapted to the needs of the individual patient. This sometimes means an increase, sometimes a decrease, in pressure.

Sollmann (143) holds a similar opinion regarding the diuretic action of the drug.

In Eggleston's (47) most recent paper on digitalis, he says:

> While it has been claimed that digitalis exerts a specific diuretic action on the kidneys, or that it produces diuresis by selective vasodilatation of the renal arterioles, the evidence for these claims is quite unsatisfactory, and careful studies have shown conclusively that the drug is not a diuretic in normal animals. It has also been observed repeatedly that no diuresis follows the administration of digitalis to normal human beings or to those with heart failure uncomplicated with edema or serous effusions. In cases of nephritis with edema, or even with general anasarca, digitalis also produces no diuresis when heart failure is not associated with the nephritis.

When, however, heart failure is accompanied with edema or anasarca, profuse diuresis may follow the administration of digitalis, but this is found to occur only when the heart failure is more or less effectively overcome by the drug, and when the heart failure is not affected, no diuresis ensues from its administration. It is clear, then, that the diuretic action of digitalis in man, is essentially secondary to its capacity to relieve heart failure and restore the circulation; and when it is effective in edematous cases of heart failure, it is often one of the earliest of the manifestations of the action of the drug, though other evidences can be detected if looked for. When adequate digitalization fails to produce diuresis in a patient with edema and heart failure, it will almost invariably be found that either the heart failure has not been relieved or that the failure is complicated by nephritis, which then demands appropriate treatment.

At variance with Eggleston's idea regarding the relation of nephritis to digitalis diuresis are the findings of Hedinger (quoted by Edens, 37) that digitalis has a direct diuretic action on the diseased kidney, which is independent of its action on the heart. However, there is considerable chance for differences of opinion as to what is meant by a diseased kidney.

The idea that pathological changes may influence the effect of digitalis on the kidneys appears again in a recent paper by Jarisch (84). He reports two cases of syphilitic aortitis in which diuresis was inhibited by therapeutic doses of digitalis but was increased by very small doses. Jarisch makes use of an idea of Meyer (113) in order to explain these results that increased excitability of the renal vessels lowers the threshold for both the vasoconstricting and vasodilating action of digitalis. He suggests that both patients had increased excitability of their renal vessels as the result of the incipient stage of contracted kidneys that was present. He states that his findings are in accord with those of Meyer who found that in early nephritis diuresis was produced by smaller doses than when the kidneys were normal. Jarisch considers that small doses of digitalis should be used when nephritis is present, and that caution as to dosage should be used in heart cases that have low specific gravity of the urine, which points to renal sclerosis.

The relation of the output of urine and alterations in blood pressure has been studied by Lawrence (91) who found that in his 26 patients,

diuresis was always accompanied by a fall in blood pressure, and 88 per cent of the cases showing a fall of blood pressure had diuresis. These findings, although of interest, do not, at present, add evidence of value in determining the manner of production of diuresis by digitalis.

The question as to a primary or direct action of digitalis on the kidneys or its vessels in cases of cardiac failure with edema, should be considered as yet unsettled, although it has been abundantly demonstrated that digitalis has no diuretic action except under very special conditions.

Cohn (20) has reported that a diminution in the output of urine is sometimes seen when well marked toxic symptoms appear. This phenomenon is adequately accounted for, he believes, by the presence of nausea and vomiting, which diminishes the fluid intake and may result in the loss of considerable fluid by emesis. This observation is confirmatory of a statement by Withering who said that large doses of digitalis may check the flow when smaller doses had increased it.

IX. THE USE OF DIGITALIS IN HEART FAILURE

Digitalis has attained the reputation of being the most valuable drug in the treatment of heart disease, and by the term heart disease is usually meant a group of symptoms such as dyspnea, cough, chest pain, edema, cyanosis, weakness, and palpitation. These symptoms are in reality not evidence of heart disease, but of heart failure, and they occur as a group only when the heart is unable to maintain the normal circulation of the blood. Heart failure may result from a variety of cardiac disorders; some of which are much more susceptible to a favorable influence by digitalis than others. The great reputation of the drug in heart disease doubtless rests upon the striking benefits which it produces in cases of heart failure dependent upon one particular type of cardiac derangement. On the other hand, fault has been found with the drug when it has been used in heart failure dependent upon other causes with the expectation that similar results are to be obtained. In considering the therapeutic use of digitalis, it is just as necessary to take into account the various cardiac derangements responsible for heart failure as it is the effects produced by the drug.

In fact, it is only when these two aspects of the subject are brought together that a rational basis for the therapeutic use of the digitalis bodies can be established. It is undoubtedly because clinicians have not fully understood the action of digitalis and because pharmacologists have not fully understood heart failure, that so many misconceptions have existed in the past regarding the therapeutic use of digitalis. The coöperation of clinicians and pharmacologists which has recently come about has been responsible for some of the most valuable contributions to the present-day knowledge of digitalis. Examples of this coöperation and collaboration are those of Mackenzie and Cushny in England and of Eggleston and Hatcher in America. This type of coöperative work is greatly to be desired, and is destined to bring forth results of great value in many fields of medicine.

1. Classification of heart failure

In the following part of this review, the relative value of digitalis will be discussed in the various disorders of the heart which are commonly seen; and which may lead to the failure of that essential organ to maintain an efficient circulation of the blood. Cohn (20) has emphasized the desirability of considering the action of digitalis in its relation to various forms of heart failure, which he has divided for this purpose according to the following table.

A. Normal rhythm.....	a. Without edema	1. With normal blood pressure	
		2. With high blood pressure	
	b. With edema	3. With normal blood pressure	
		4. With high blood pressure	
B. Auricular fibrillation ..	a. Without edema	5. With normal blood pressure	
		6. With high blood pressure	
	b. With edema	7. With normal blood pressure	
		8. With high blood pressure	

This classification shows the importance Cohn has placed upon the type of cardiac rhythm, the presence of edema and the state of the blood pressure in the reaction of the heart and circulation to digitalis. He has discussed his observations on the action of the drug in patients with normal cardiac rhythm, without edema and with normal blood

pressure; and a comparison of the action of the drug in these patients with those in other groups has led him to conclude as follows:

> It seems important to emphasize the fact that it is essential to distinguish differences which patients suffering from heart disease present and to study them in groups, with these differences in mind. Rhythm certainly offers a prime basis. The effect of digitalis on rate and on a number of other capacities varies with the nature of the disturbed function.

In actual practice, it is often impossible to classify sharply cases of heart failure on the basis of the derangements of function underlying their production. Nearly every case results from a combination of causes, and these causes must be evaluated relatively to one another, in any attempt to arrive at a clear understanding by which treatment may be intelligently instituted. The ability to determine the relative importance of the various factors underlying the production of heart failure is an essential requirement for its successful treatment. The disorder of the heart revealed most prominently by all the means of examination now available may often be unimportant or only contributory in the production of heart failure in any particular case. The relative importance of valvular and muscular lesions of the heart may be cited as an example. In many cases, a valvular defect obtrudes itself upon the physician, while muscular inefficiency, so difficult or impossible to determine directly, is in reality the actual cause of heart failure. It is necessary to point out the difficulties regarding the classification of heart failure on the basis of its causation, because a discussion of the effects of digitalis in this relation to the various disorders of the heart cannot take into account many of the practical problems involved in the use of the drug in the treatment of heart failure. These can only be solved by the careful study of patients, in whom a great variety of conditions and circumstances are encountered, calling forth constantly the exercise of clinical judgment, which cannot be acquired from books, but only at the bedside or in the consulting room.

2. Disturbed cardiac mechanism

a. Auricular fibrillation. Following the suggestion of Cohn, rhythm is taken as a prime basis for distinguishing the various types of

disorders of the heart, and those disorders associated with or consisting of disturbed cardiac mechanism will be considered before those with normal mechanism and regularly beating hearts are taken up. It seems desirable to adopt this order and to discuss first the use of digitalis in auricular fibrillation, because it is in this type of deranged cardiac rhythm that digitalis produces its most brilliant results, a point which it is well to emphasize at the outset.

A clear understanding of auricular fibrillation is essential for the intelligent employment of digitalis. It has been especially well described by Lewis (100, 101), to whose work the reader is referred.

The salient features by which this condition is recognized may be summarized as follows: The pulse and the cardiac sounds occur irregularly without any order to the arrhythmia, and usually with a considerable increase in rate. There is no evidence of the normal auricular contractions in the veins of the neck, as shown by polygrams, and the auricular waves, the so called P waves, of the electrocardiogram disappear. A constant succession of small waves may sometimes be seen in the venous pulse curve, while the electrocardiogram shows almost constantly a series of small rapidly recurring waves, lacking uniformity and well defined form, seen throughout the diastolic portion of the curve. All these phenomena are readily appreciated when it is realized that the auricles no longer contract as a whole in a rhythmical fashion, but stand in diastole with their separate fibers contracting and relaxing one after another constantly. This abnormal type of auricular action sends down impulses to the ventricles more frequently than the normally beating auricles and the rhythmical character of the impulse formation is lost. A rapid irregular ventricular action therefore results which is distinctly less efficient in the maintenance of the circulation than is the slower regular normal beat. This increase in rate is often an important factor in the failure of the heart when auricular fibrillation is present.

Auricular fibrillation was recognized as a common disturbance of the human heart-beat in 1909, when Rothberger and Winterberg and Lewis simultaneously demonstrated its existence by means of electrocardiograms. Several years previously, however, Mackenzie (108) drew attention to the fact that there were striking differences in the effects of digitalis in cases with irregular heart action and in cases

with regular rhythm, and he stated that "no rational idea of the manner in which digitalis acts can be obtained unless this change in the heart's action is appreciated." He was also perhaps the first to study the effect of digitalis in patients with auricular fibrillation after this condition became established as a clinical entity. His paper which appeared in 1911 was followed shortly by important contributions by Cushny (29) and Edens (37) and, since that time, the value of digitalis in this condition has been generally recognized. It is scarcely necessary to review the papers of other students of this subject, such as Fahrenkamp (52), Fulton (56), Christian (14), Robinson (128), Weil (153), Cohn (20), Borultau and Stadelmann (7), Pratt (122), Wedd (152) and others who have all borne witness to the striking benefits obtained by the use of digitalis in auricular fibrillation. Their papers are referred to in regard to special phases of this subject.

It has been repeatedly shown that the great value of digitalis in auricular fibrillation lies in the fact that the drug slows the abnormally rapid and irregularly beating ventricles, and this effect of the drug is generally considered its most important accomplishment. Lewis (99) has recently expressed what is perhaps an extreme view of this matter. He says:

> The chief value of digitalis lies in the power to control the ventricular rate when fibrillation of the auricles has come. In most patients in whom this disorder of the heart is discerned, the ventricles beat rapidly, at rates of 120, 140, 160 and even more per minute. It is this rapid action which fatigues the heart, and digitalis, by lessening the rate, lessens the fatigue. The normal heart rate, while the body is at rest—to take approximate and convenient numbers—is 60 beats to the minute. Each ventricular cycle lasts one second; of this, one-third is occupied by systole; two-thirds by the resting period of diastole. The heart works one shift and sleeps for two. But if the rate is 120 beats to the minute, then each cycle lasts half a second; systole lasts quarter of a second and so does diastole. Work and rest alternate in equal shifts. As the rate of beating rises, so is systole increased relatively at the expense of diastole. Very important is it, therefore, to reduce the heart rate when this is excessive. A chief cause of rapid heart action when heart failure threatens or has come, is fibrillation of the auricles, and it is in this condition that digitalis acts so beneficially; it reduces and holds the rate within normal bounds.

The reduction of accelerated ventricular rate is the only important action of the drug upon the human heart of which we have knowledge. There are few, if any, instances, of which we know with certainty, in which digitalis acts beneficially, except cases of accelerated action; there are few instances of acceleration in which the drug produces unquestionable benefit apart from those provoked by fibrillation of the auricles.

The principle of digitalis therapy—and when I speak of digitalis, I include the allied drugs, strophanthus and squills—is that, administered to suitable cases, the heart, by means of it, obtains rest. The giving of this drug to unselected cardiac cases is much to be deplored. Those who regard digitalis as a cardiac stimulant mistake its character; its chief action is to rest the heart. To the heart, foxglove is not tonic, but powerfully hypnotic. It controls the diastoles of the heart; it extends the period of sleep.

Although most students of digitalis do not share entirely the idea of Lewis regarding the relative uselessness of the drug in conditions other than auricular fibrillation, he has well expressed the consensus of opinion regarding its use in auricular fibrillation.

Agassiz (2) has treated a series of cases of auricular fibrillation with small doses of strophanthin administered intravenously and has shown that this drug has a very similar action to that of other members of the digitalis group when employed upon cases of auricular fibrillation. He states that it is a powerful and serviceable remedy when a rapid reduction of the heart rate is desired in cases of auricular fibrillation in young subjects or in those cases which give a history of rheumatism. The heart rate may be reduced from 180 or 160 to 100 or 80 per minute within six or eight hours. Agassiz's method of administration of strophanthin will be taken up later.

As stated previously, the slowing of the heart is brought about by a different mechanism than that by which digitalis slows the normally beating heart. When the auricles are fibrillating, stimuli are sent down to the ventricles unrhythmically and at a rate much higher than from the normally beating auricles. Digitalis depresses the conductivity of the pathway between the auricles and the ventricles, which then allows fewer stimuli to pass. In this way, the rate of the ventricles is slowed and the arrhythmia reduced. This effect is very desirable because the rapid irregular ventricular activity which

the fibrillating auricles engender is much less competent to maintain the circulation than the ventricular activity of normally beating heart. The ventricles become more competent when they are slowed and regulated by digitalis. The tumultuous action of the fibrillating auricles is not appreciably affected by digitalis as revealed by electrocardiograms. The manner in which digitalis affects the conduction of the cardiac impulse has been already considered.

The question has been raised whether other factors may not enter into the slowing of the ventricles which digitalis produces in hearts with auricular fibrillation, which are not involved in the depression of conduction in the normally beating heart. Cushny has been especially interested in this subject, and has raised the question as to whether the action of digitalis on the cardio-inhibitory centre is the important factor in slowing the ventricles in auricular fibrillation. Cushny, Marris and Silverberg (32) found that the ventricular rate, slowed by digitalis, was not restored to its original rate when the vagi were paralyzed by atropin. They came to the conclusion that in auricular fibrillation, the ventricular slowing was accomplished by other means than by stimulation of the cardio-inhibitory mechanism, which seemed to play no part in the action of digitalis in auricular fibrillation.

They believe that the conductive pathway from auricles to ventricles becomes less excitable when the nutritional condition of the tissues is improved, and that this improvement may result not only from the increased efficiency of the circulation brought about by the direct action of digitalis on the ventricular muscle, but also by lessening the demands on the heart by rest. They explain in this way the ventricular slowing which occurs when patients with auricular fibrillation are put to bed. Their hypothesis calls for the existence of abnormally increased conductivity in the hearts of patients with auricular fibrillation caused by malnutrition of the tissues. This idea is hard to accept in the light of the state of conduction in other types of heart disease in which it can be accurately determined, and is not infrequently found to be decreased.

In a later publication, Cushny (31) gives the results of further work on this subject in which he attempted to reproduce the cardiac condition of cases of auricular fibrillation in perfused hearts. He states

his belief in two independent reactions of conduction to therapeutic doses of digitalis. The first is that observed in the normal heart of experimental animals and in the normally beating human heart. It is the result of stimulation of the cardio-inhibitory centre.

The second is that observed in cases of auricular fibrillation in man, and results from the direct action of the drug on the conducting system. Cushny believes that the ventricular slowing which digitalis produces in cases of auricular fibrillation is independent of the action of the drug on the inhibitory mechanism, for it is not prevented by atropin. The primary reason why digitalis acts directly on the conducting mechanism in these cases is the malnutrition of the heart and auricular fibrillation merely favors its appearance by accentuating the fundamental cardiac malnutrition. Wedd (152) has also studied a number of cases of auricular fibrillation and has injected atropin during thorough digitalization. He has come to the conclusion that in all cases digitalis affects conduction both by its stimulation of the cardio-inhibitory centre and by its direct action on the heart, with relatively greater local action in auricular fibrillation. Exception is taken to the statement of Cushny that in fibrillation there is no digitalis action through the inhibitory mechanism. Eggleston (47) has recently discussed Cushny's experiments and conclusions and is in substantial agreement with Wedd.

It is well known that some cases of auricular fibrillation are unusually susceptible to digitalis. Robinson and Draper (132) have shown that in cases of auricular fibrillation prolonged stoppage of the ventricles may be brought about by pressure over one of the vagi of the neck. Weil (154) has also found vagus pressure more effectual in auricular fibrillation than in other conditions, a result which he attributes to an impaired state of the heart. He also found that the normally beating hearts of patients to whom digitalis had been given were more apt to respond to vagus pressure by depression of conduction than were the hearts of untreated patients. Weil believes that digitalis stimulates the cardio-inhibitory centre and, at the same time, renders the conducting system more susceptible to the influence of the vagi. Fahrenkamp (52) found that in cases of auricular fibrillation pressure over the vagus nerves was sometimes effectual in stopping the ventricles after the administration of digitalis in cases in which

vagus pressure was ineffectual before the drug was given. These findings suggest that the conduction mechanism is rendered more susceptible to vagus action by digitalis, which is in accord with the experimental results of von Tabora (148).

Hirschfelder (80) investigated the action of the drug on dogs in which auricular fibrillation was produced by faradization and found that the irregularly beating ventricles were markedly slowed by digitalis, but the rapid arrhythmia promptly returned when the vagi were paralyzed by atropin. Further slowing was obtained by very large doses of digitalis after atropin had been given and complete heart block with slow ventricular rhythm could be induced. Cushny (31) performed similar experiments with cats and found that after the vagi had been cut, strophanthin failed to remove the irregularity and acceleration of the ventricles until a late phase of the action of the drug set in, with auriculo-ventricular dissociation. He contends, however, that these experiments are not comparable to auricular fibrillation in man in which malnutrition of the cardiac tissues presumably exists.

It has been suggested that digitalis is especially potent in blocking impulses sent down by the fibrillating auricles. In order to determine whether this is true Robinson (127) studied the effect of vagus stimulation in dogs, both with normally beating hearts and with auricular fibrillation induced by faradization of the auricles. The results were recorded by electrocardiograms. The experiments show that the type of auricular activity has no influence on the degree to which impulses are blocked by vagus stimulation. In the light of these experiments it would seem that the character of the auricular activity, whether coördinated or fibrillary, plays no part in the effectiveness of digitalis in depressing conduction by stimulation of the cardo-inhibitory centre.

An examination of the evidence bearing on the question of the manner by which digitalis reduces the ventricular rate in auricular fibrillation must lead to the conclusion that various phases of the subject remain unsettled, and little or nothing is known regarding certain of its aspects. It seems established that the ventricular slowing is brought about by the dual action of digitalis on the cardio-inhibitory centre and directly on the conduction pathway, but the

relative importance of these two effects is not clearly understood. Furthermore, it is not yet determined to what extent cardiac malnutrition or other changes in the heart influence the action of the drug, nor what relation exists between the ventricular slowing in cases of auricular fibrillation produced by bodily rest and that caused by digitalis. A clearer understanding of these problems would doubtless place the use of digitalis in auricular fibrillation on a more intelligent basis, and would probably lead to its more effectual employment.

There is some evidence in favor of the belief that digitalis may be beneficial in cases of auricular fibrillation independent of the ventricular slowing it produces. Edens (37) for instance, has observed clinical improvement without any diminution of the ventricular rate. Increased efficiency of the ventricular contraction by the direct action of the drug on the heart muscles may play some part in its valuable effects in this condition.

Patients with auricular fibrillation are not all equally susceptible to the beneficial effects of digitalis. The cases may be roughly divided into two groups, those in which auricular fibrillation follows the so-called rheumatic infections and those in which arterial sclerosis, with presumably accompanying cardio-sclerosis is present, and frequently with a preceding syphilitic infection. The first group is composed, as a rule, of young or middle aged persons who show very rapid ventricular rates. Cases of this group are, as a rule, those that show the most striking benefit from digitalis. The cases of the second group may be much less benefited. They do not show such high ventricular rates, and, in some cases, it is not above the average normal level, although evidences of heart failure are well defined. Mackenzie (109) who first pointed out this distinction, attributed the difference to changes in the cardiac muscle, and holds that the reaction to digitalis is much more easily induced in cases with presumably slight myocardial damage than in cases with extensive degeneration. This distinction is undoubtedly correct, but it does not take into account the state of the conduction pathway, which is presumably more damaged in the second group of cases than in the first. Digitalis is often of little value in cases in which the ventricular rate is slow before digitalis is given. In these cases, the tissues involved in the

conduction of the cardiac impulse are damaged and are therefore not capable of transmitting impulses at a rapid rate. This damage may be taken as an evidence of a widespread involvement of the myocardium which is unable to maintain an efficient circulation even when the ventricles are contracting slowly. Under these circumstances, further slowing may cause no improvement in the circulation, and sometimes may be distinctly harmful.

On the other hand, in many cases of auricular fibrillation, the myocardium is sufficiently preserved so that the ventricles can maintain the circulation efficiently when their rate is held within bounds by digitalis. Certain conclusions regarding prognosis are justified therefore from the response to the drug. Patients should be studied with this point in mind. Physicians should also learn to distinguish between cases in which excellent results are to be expected from those less liable to benefit, before drawing conclusions as to the efficiency of the preparation of the drug being used.

The ventricular rate, in many cases, can be regulated at will by the amount of digitalis administered. The optimum rate and the doses required to maintain it, must be determined by trial in each case. The dosage has to be varied frequently, and no rule applies to all cases. The proper amount of the drug to be given is to be determined by the effect of various doses on the symptoms of heart failure and by the ventricular rate.

It must be borne in mind that the radial pulse cannot be relied upon for determining ventricular rate, as when the ventricles are beating rapidly and irregularly, many contractions may fail to produce a palpable pulse at the wrist. For this reason the ventricular rate should always be determined by counting the number of heart beats per minute by means of the stethoscope. It is very useful in following the effect of digitalis in auricular fibrillation to determine the number of ventricular contractions that fail to produce a palpable pulsation at the wrist. The number of such beats per minute constitute the so-called pulse-deficit, a term invented by George Draper (personal communication). A pulse deficit of 20, 30 or more a minute is often found in untreated cases, and the disappearance or reduction of the pulse-deficit should be taken as an important guide for the proper dosage of digitalis.

It is usually desirable to reduce the ventricular rate to between 70 and 80 beats per minute, although some cases seem to have a better state of cardiac efficiency when the rate is higher, and Pratt (122) has found that the circulation is sometimes best maintained at a rate much lower than that of the normal heart. In one of his patients under constant administration of digitalis, the heart rate was rarely above 50 per minute during a period of two years.

The constant employment of digitalis is usually necessary to keep the ventricular rate continuously slowed, and the benefits of constant use of digitalis have been pointed out by Schmoll (141), Borultau and Stadelmann (7), Fulton (56), Pardee (117) and others. Pardee has brought out the fact that the body must be kept nearly full of digitalis and not nearly empty, and in order to accomplish this, the drug must be given at a rate comparable to that of its elimination from or destruction in the body. Fulton (56) remarks that many cases need continuous administration of the drug and by the use of small doses the heart may be controlled so that the patient may be able to go on with his ordinary routine of life indefinitely.

It is certainly one of the most gratifying experiences in medical practice to see the great benefit digitalis frequently brings about and maintains in these patients for months and years by its constant administration in doses so regulated that toxic symptoms do not appear, while the heart is kept continually under its influence.

Excessive amounts of digitalis in auricular fibrillation may produce complete heart-block, causing the ventricles to assume a regular rhythm at an excessively slow rate. Taussig (149) has reported two such cases in which permanent complete block developed during digitalis administration. Slow regular ventricular action occurring in cases of auricular fibrillation during digitalis medication should always be taken as an indication of excessive action of the drug and should lead to its discontinuance. Complete heart-block may occur without other evidences of intoxication, as happened in a case reported by Robinson (128).

Another disturbance of the heart beat which is prone to follow the administration of the drug in cases of auricular fibrillation is the so-called bigeminal pulse or coupled rhythm. It may appear when relatively small amounts of the drug have been given, which do not

ordinarily produce toxic symptoms. The absolutely irregular rhythm is replaced by pairs of beats followed by pauses of varying lengths. There is usually a fairly constant time relation between the coupled beats. Coupled rhythm may be suspected by the study of the heart sounds and radial pulse as Christian (14) has stated, but electrocardiograms reveal their true nature. Coupled rhythm is produced by the occurrence of a premature contraction of ventricular origin following regularly each ventricular beat stimulated by the auricles. Its occurrence is to be taken as a sign for discontinuing digitalis.

Edens and Huber (38) have studied this phenomenon and consider that it probably only occurs in hypertrophied insufficient hearts. They regard its occurrence with relatively small amounts of digitalis as an unfavorable prognostic sign. They found that coupled rhythm was always dependent on ventricular premature contractions which resulted, they believed, from an increase in the irritability and stimulus formation in the ventricles produced by digitalis in damaged hearts where there was a high calcium content in the blood. The amount of the drug producing coupled rhythm was quite variable.

The beneficial action of the drug on the peripheral circulation in auricular fibrillation has been demonstrated by Stewart and Scott (145) who studied the blood flow in the hands by means of calorimeters. They found that in three of four cases, the blood flow was increased in the hands within twenty-four hours after the tincture of digitalis was given. This finding is merely a quantitative corroboration of the effects of the drug when determined by the clinical study of signs and symptoms of heart failure.

The striking action of the digitalis bodies in slowing the ventricular rate in auricular fibrillation has been put to useful purposes in studying certain aspects of the digitalis problem, as the ventricular slowing usually occurs as a sharply defined reaction on the part of the heart which may be readily distinguished as of digitalis origin, the onset and duration of which can be determined.

b. Auricular flutter is a disturbance of the heart beat caused by an excessively rapid auricular rate, usually about 300 contractions per minute, accompanied by varying degrees of heart-block. Recent studies of Lewis, Feil and Stroud (102) indicate that auricular flutter is in reality closely allied to fibrillation. They interpret the very

rapid auricular activity as dependent upon a continuous circuit of the cardiac impulse through the auricles, along a constant path at a rate constant for each case. They account in this way for the practically absolute regularity of the auricular rhythm which they have demonstrated, and for other features of this cardiac disorder. The ventricles do not participate in the excessive auricular rate, but may respond to every second, third or fourth auricular contraction. Flutter generally persists for months or years, and does not tend to cease spontaneously. The recognition of auricular flutter can be readily accomplished by electrocardiograms and less easily in polygraphic tracings. Without the use of graphic methods, it cannot be distinguished with certainty.

Digitalis has proved of definite value in treating cases of auricular flutter. Lewis (96) first showed conclusively that flutter passed into fibrillation during the administration of the drug, although Mackenzie (108) and Turnbull (150) had previously recorded cases of the same nature. In a later paper, Lewis (97) recorded other instances of this action of digitalis, and has pointed out that when fibrillation surplants flutter it is usually temporary and the normal cardiac rhythm may be resumed permanently. These observations have been frequently confirmed, and Lewis states that the production of fibrillation by digitalis administration is an important therapeutic measure in cases of flutter. The action by which auricular flutter is transformed into fibrillation is uncertain. The drug renders the auricles more liable to fibrillation than before, and this may be accomplished either by direct action on the auricular tissues or by its action through the vagi. It seems possible that the conduction of impulses through the auricles is interfered with and areas of block are produced, a change which is, according to recent investigations, an important factor in the causation of auricular fibrillation. When first set up, fibrillation tends to disappear, and in the cases under discussion the normal rhythm is resumed before fibrillation becomes, so to speak, firmly established. Lewis has shown that auricular flutter may be abolished by the administration of digitalis after it has persisted for months.

Digitalis may serve another useful purpose in auricular flutter as Lewis has also pointed out. With the auricular rate as high as 300 per

minute the ventricles may respond to every second contraction, and so attain a rate of 150 beats per minute. Digitalis by its action on the conduction pathway between auricles and ventricles may increase the degree of heart-block which is already present, presumably because of the excessive auricular rate. After the depression of conduction the ventricles may respond to only every third or fourth auricular contraction and so be decidedly reduced in rate, much to the improvement of the cardiac efficiency. Thorough digitalization of patients with auricular flutter is therefore a valuable procedure whenever this disturbance of the heart beat is encountered.

c. Cardiac contractions of abnormal origin. Impulses leading to cardiac contractions may arise in some point in the auricles or ventricles quite outside the region of the heart in which the normal rhythmical stimuli are generated. Such impulses may arise occasionally or frequently at fairly regular intervals causing the single premature ectopic beat, or extrasystole, or they may arise rhythmically and so rapidly that they dominate the cardiac rhythm causing a high grade of tachycardia. These various conditions dependent upon cardiac contractions of abnormal origin will be discussed separately in their relation to the action of digitalis.

Premature contractions or extrasystoles occur in association with various cardiac disorders, as well as in hearts that show no other abnormalities. They have no material influence on the circulation when occurring only occasionally, but when frequent, as often for instance, as every second or third regular heart beat, they tend to lower the efficiency of the heart, often produce annoying subjective symptoms and are therefore undesirable. There are two questions that arise concerning the relation of digitalis to premature contractions. Has the drug any effect in preventing their occurrence and is their spontaneous occurrence a contraindication to the therapeutic use of the drug?

It has long been known that large doses cause premature contractions which are recognized as one of the most constant manifestations of the influence of the drug on the heart, and as such have been discussed previously. Although Wenckebach (155) was aware of this effect of large doses, he reported several cases, and published curves of two of them in which small doses of digitalis caused the disappearance

of premature contractions after they had been present over long periods of time. He considered this effect as due to the direct action of the drug on the heart muscle. Mackenzie (109) has given digitalis to patients in whom spontaneous premature contractions of ventricular origin were occurring and was unable to observe any effect on them.

Edens (37) has perhaps studied the subject more closely than any one else. He reports the results of the use of digitalis in a variety of cases with premature contractions, and he has attempted to differentiate these cases on the basis of the possible causation of the premature beats. He concludes that premature contractions dependent upon recent rheumatic lesions of the heart are not influenced while those that appear to be associated with insufficiency of the coronary circulation are probably cleared up by digitalis. He found that the type of premature contractions that occur in persons who use tobacco excessively, the so-called nicotine extrasystoles, are not affected by the drug, and those occurring in nervous persons sometimes disappeared and sometimes were unaffected by digitalis. Edens considered that the variable effects are dependent upon the fact that there are different forms of premature contractions and that sharp differentiation on the ground of further experience is urgently needed. He considers that premature contractions should be taken as contraindications for the intravenous use of digitalis.

So little is known regarding the underlying causes of ectopic premature contractions that a satisfactory hypothesis regarding the means by which digitalis may effect them and the manner in which they may respond to the drug cannot be put forward. It is possible that the heart muscle may be rendered less irritable by the stimulation of the cardio-inhibitory centre, as Wenckebach (155) has suggested. The production of premature contractions by the direct action of the drug probably occurs in hearts not already disposed to them only after very large doses, approximately 50 per cent of the minimum lethal dose. It is possible therefore that this action does not come into play even in hearts showing spontaneous premature contractions, while other effects of the drug tend to cause their disappearance. Their presence should not be taken as a contraindication for the therapeutic use of digitalis, although it should lead to caution, and

should indicate a reduction of dosage. The favorable influence of digitalis in bringing about the disappearance of premature beats is not to be viewed with any great expectations of success, although in small doses it may have this effect in some cases. Christian (19) has stated that

> this question of the exact relation of digitalis to extrasystoles is one still under discussion. In most cases, extrasystoles are more an incident in, rather than a cause of cardiac decompensation and their presence can be neglected in considering the probable efficiency of digitalis therapy.

d. Paroxysmal tachycardia has been shown by electrocardiographic studies to be a disturbance of the heart beat dependent upon a mechanism closely allied to that responsible for the occurrence of single premature contractions. It is characterized by the sudden onset of a very rapid cardiac rate, usually between 150 and 250 beats per minute, which terminates as suddenly as it begins, the rate usually returning to normal after a period of some hours or days. Very short paroxysms are also seen. These periods of tachycardia are apt to recur, once they have been established. The tachycardia is brought about by the production of cardiac impulses in some point removed from the region of normal impulse formation. The ectopic focus generates impulses at an abnormally rapid rate, and assumes the rôle of cardiac pace-maker. The ectopic focus is usually in one of the auricles but ventricular foci have also been found to produce such paroxysms.

Digitalis has proved to be without influence on the high rate of the heart brought about by this disturbance of its mechanism. Edens (37) has reported a case in which the paroxysm stopped during digitalis administration, but the relation of cause and effect cannot be established. During the attack the degree of heart failure varies greatly from patient to patient; but, in most instances, when the attacks are not prolonged, the evidence of cardiac insufficiency is not marked. Individuals who have these paroxysms of tachycardia not infrequently show no definite evidence of heart disease between attacks, and have, presumably, hearts that can adjust themselves to the abnormal rate. In prolonged attacks, however, the heart may show signs of muscular fatigue, which may be considered as an indi-

cation for the use of digitalis. Robinson and Hermann (133) have recently reported a case of prolonged tachycardia of ventricular origin in which digitalis was given without any beneficial effects.

e. Heart-block. The depression of conduction is one of the most definite effects which digitalis produces, as has already been brought out. Therefore in partial heart-block, when further interference with the passage of the cardiac impulses from auricles to ventricles is decidedly undesirable, digitalis is contraindicated.

Cases are occasionally seen in which the conduction time is lengthened on account of faulty nutrition of the functional tissues between the auricles and ventricles. This depression in conduction is comparable to that which occurs during asphyxia, and may disappear with an improvement in the state of the circulation. In these cases digitalis has been observed to bring about an improvement in the auriculo-ventricular conduction, and to shorten the conduction time to within normal limits. Careful study by those experienced in abnormal cardiac physiology is necessary to differentiate these cases from those showing depression of conduction produced by structural changes in the conducting system.

In complete heart-block, when the ventricular contractions are being stimulated by the inherent rhythmicity of the ventricles, the action of the drug on conduction may be disregarded. Under these conditions an improvement of the efficiency of the ventricles and especially the quickening of their slow rate is the result to be desired, and there is evidence to show that this may sometimes be attained by digitalis.

Jagic (82) noted improvement of a patient with complete heart block when small doses of digitalis (0.05 gram per day) were given. Martinet (110) has also advocated the use of digitalis in complete heart-block, and has warned against its use when the block is partial. He believes that digitalis acts both on the vagi and directly on the heart muscle, and he points out that the latter action may be effectual in complete heart-block while the independently beating ventricles are not under the control of the vagi, and so the former action can be disregarded. Bachmann (3) has studied a case in which strophanthus was given with beneficial results and with an increase in the ventricular rate while the auricles were slowed. Bachmann (4)

reported a second case with similar results, in which the ventricular rate increased from 23 to 31 beats per minute during the administration of the drug. He is of the opinion that strophanthus is of more benefit in complete heart-block than digitalis.

Hewlett and Barringer (79) report a case in which digitalis produced auriculo-ventricular dissociation and in which the ventricular rate exceeded that of the auricles. They suggest on the basis of this observation that the drug may be of value in complete heart-block. They failed, however, in the one case that afforded them an opportunity of testing their hypothesis to get any increase in the ventricular rate following the administration of digitalis.

Cushny (29) has suggested that helleborein might be especially useful in heart-block, as he says it has an effect on the heart muscle similar to that of digitalis, but is without effect on the cardio-inhibitory mechanism. Recent investigation of cases of complete heart-block have shown that the rate of the independently beating ventricles is, in most instances, free from the control of the vagi, and therefore the inhibitory action of digitalis should not be considered of moment in these cases. The direct action of the drug on the heart muscle may be advantageous in increasing the output of the heart even without a change in rate. Complete heart-block is not a contra-indication for digitalis according to Mackenzie (108) but the drug should be withheld in cases of temporary heart-block where a return of the normal heart beat is anticipated.

3. Heart failure with normal cardiac mechanism

a. Myocardial insufficiency is the name now frequently applied to that form of heart disease in which the power of the heart muscle is apparently impaired, and in which no other cause can be discovered to account for the failure of the heart to maintain the circulation adequately. The term myocarditis has been used to express the same condition, but myocardial insufficiency is to be preferred, as it expresses functional rather than structural damage of the heart. In many instances, no satisfactory explanation can be found by the present day methods of examination of tissues for obvious myocardial inefficiency on the basis of structural changes in the heart muscle.

In the cases under consideration, ample evidence of heart failure is present, while there is no conspicuous disturbance of the cardiac mechanism, no demonstrable structural damage to the valves, no alterations in the vascular system sufficient alone to account for the symptoms. The patients, who are usually past middle life, are short of breath, unable to lie flat in bed and often have anginal pain, especially on exertion. They frequently have edema and cyanosis, evidence of congestion of the lungs and liver, with hydrothorax and, at times, ascites.

The heart is enlarged and the character of the heart sounds may be altered. There is often a systolic murmur at the apex. The urine usually contains albumen and casts, and there may be other evidence of renal insufficiency. The blood pressure is frequently elevated and the heart rate is often increased.

The clinical picture may vary considerably and only the most obvious symptoms have been enumerated in order to define this frequently encountered condition. The value of digitalis in the type of myocardial insufficiency that has been described is not nearly so well established as it is in cases of heart failure with auricular fibrillation. This is to be expected, as heart failure in these cases is dependent upon some fundamental change in the cardiac muscle which no known means can remove; while in auricular fibrillation a definite factor of heart failure can be altered advantageously. The difference in the effects of digitalis in these two types of heart disease is noted consistently in the literature on digitalis since it was first brought out by Mackenzie (108) in 1905, and since these types have received definite clinical differentiation.

The prime object in the use of digitalis in myocardial insufficiency is to improve the ability of the heart in propelling the blood and in restoring the balance between the arterial and the venous side of the circulation. It has already been shown how difficult it is to obtain any definite direct evidence of changes in the output of the heart. Various elaborate methods have been devised for its indirect determination, but these have not been extensively used in the study of the problem now under consideration. It is necessary therefore to rely on the improvement of symptoms by digitalis, and this evidence is often difficult to evaluate.

It has been repeatedly shown by Cushny (29), Mackenzie (109), Edens (37), Pongs (120), Cohn (20), Pratt (122), Christian (16) and others that the cardiac rates of these cases is usually not slowed by digitalis, and the action of the drug on the cardio-inhibitory mechanism apparently plays as a rule no part in the favorable results which the drug may accomplish in cases with regularly beating hearts. Cohn (20) has emphasized the importance of differentiating cases with edema from those without it, and there is general agreement that in cases of myocardial insufficiency with edema, diuresis follows the administration of digitalis, the edema is diminished or disappears and there is a general improvement in symptoms. At the same time, the idea prevails, as recently stated by Eggleston (47) that the diuretic action of the drug is essentially secondary to its capacity to relieve heart failure and to restore the circulation. Diuresis must be looked upon, if this idea is correct, as evidence of a beneficial influence of the drug on the heart muscle, although this conclusion is not as yet warranted as final. This question has already been discussed.

The various statements of those who have studied properly the effect of digitalis in myocardial insufficiency indicate that benefit is often derived from its use, but the manner of its action is still obscure. Cushny (29) noted improvement in such symptoms as dyspnea, cyanosis and edema without any change in the cardiac rate, and attributed the improvement to the direct action of the drug on the heart muscle. Edens (37) also observed clinical improvement without slowing of the heart rate, and he believes the contractility of the heart is effected favorably by digitalis, but considers that myocardial damage limits its influence in this regard. Cushny's (31) later work emphasizes the relation of malnutrition of the heart to the action of the drug, and he believes the drug is more likely to act directly on the heart when malnutrition is present. Mackenzie (109) has always been skeptical regarding the idea that heart failure may be relieved by the effect of the drug on the heart muscle. Christian (15) in discussing what he terms chronic myocarditis says that it constitutes a group of cases in which digitalis is very effective, whether auricular fibrillation is present or not, but with recurrences of heart failure the drug becomes less and less able to bring relief. Windle (162) has also observed definite improvement in the cases under

discussion, but says that the improvement in advanced cardiac failure is often only temporary, and the drug becomes less and less effective as the cardiac inefficiency advances. Christian (16) has recently reported a series of cases of myocardial insufficiency with regularly beating hearts and with edema in which digitalis produced satisfactory effects.

Pratt (122) has employed strophanthin intravenously in these cases, and says that as improvement has occurred in forms of heart failure that are rarely, if ever, relieved by digitalis, it is suggested at least that strophanthin given intravenously exerts an effect on the contractility or tonicity of the heart muscle that is not obtained from digitalis in therapeutic doses. West and Pratt (156) have recently remarked that there is little doubt in the minds of most clinicians that much good can be expected from proper dosage in patients showing regular rhythm, when their symptoms are evidence of heart failure. They gave full doses of dried aqueous extract of digitalis to a number of such patients and in many obtained effects that were quite as gratifying as in those showing auricular fibrillation.

The heart is often unusually susceptible to digitalis in the class of cases under consideration, and toxic effects may be produced by relatively small doses, so that careful study of these cases is especially necessary when digitalis is administered. It is evident that digitalis is of definite value in cases of heart failure dependent upon myocardial insufficiency, especially when edema is present. The manner in which the drug acts is still a matter of uncertainty. The fact that abnormalities exist in the heart which have not as yet been closely duplicated in animals renders comparison with experimental results unwarranted. The influence of digitalis in cases of myocardial insufficiency needs further study.

b. Pulsus alternans, a phenomenon dependent upon myocardial weakness, consists of an alternation in the regularly beating heart of relatively strong and weak cardiac contractions which gives an alternating character to the radial pulse. This abnormality of the cardiac contractions is a grave sign of myocardial insufficiency. It has been observed following the administration of digitalis, apparently as an effect of the drug; and as such it has already been considered as a toxic effect. Questions have been raised as to whether the

presence of pulsus alternans is a contraindication for the use of digitalis and what effect the drug has upon it when already present. Windle (162) has made an extensive study of these questions. He considers pulsus alternans as being invariably the expression of an overtaxed heart, and says that it is the only form of pulse rhythm giving definite information regarding the functional efficiency of the heart. Windle was among the first to demonstrate the fact that the presence of pulsus alternans is to be considered a sign of impending death, even when circulatory failure is not extreme. He has studied the effect of digitalis in over 100 cases of heart failure showing alternation, and although the condition does rarely follow the administration of the drug, he never found that digitalis increased the alternation of the pulse or produced harmful effects when it was present. On the contrary the alternation and irregularity in rhythm of the pulse frequently became lessened, and not seldom was abolished. The presence of high blood pressure does not contraindicate the use of the drug in these cases. Windle points out the relation of rate to alternation, and shows that as the diastolic periods of cardiac rest lengthen, the tendency to alternation of contractions diminishes. On the other hand, the slower the rate at which alternation is observed, the more serious is the prognostic significance, as the more extensive exhaustion of the heart muscle is indicated. Pulsus alternans may disappear permanently under digitalis in cases of myocardial damage following rheumatism, but Windle believes it practically never permanently disappears in aged patients. Christian (14) who publishes some excellent records of pulsus alternans, has obtained good results in patients showing this phenomenon. He reports a case in which digitalis produced striking slowing with definite clinical improvement, but without disappearance of alternation. Christian remarks that it is to be remembered

that a pulsus alternans is a sign of a very much impaired myocardium, and when the myocardium is greatly impaired the likelihood of functional improvement from digitalis is much decreased. To push digitalis in such a case may do much damage. Here it is particularly difficult to judge how far to carry digitalis therapy if no evident effect is produced. It would seem that in many of these cases the margin between no therapeutic effect and a serious toxic effect is a very narrow one.

Windle, in the light of an extensive experience, advises, on the other hand, to continue the drug until vomiting or coupled rhythm occurs.

4. Valvular heart disease

Valvular heart disease as such is not an indication for the employment of digitalis. Much misconception has been prevalent in medical practice regarding this fact. On the other hand, many cases with structural changes in the valves are much benefited by digitalis when heart failure follows or accompanies valvular defects. No one can conceive that the condition of the valves can be altered by the drug, and the presence of a valvular murmur, even when it is dependent upon a structural change in a valve, is never to be taken as a reason for giving digitalis. Experimental destruction of one or more of the heart valves in animals is not followed, as a rule, by marked disturbances of the circulation. However, under these conditions, the heart is otherwise undamaged, and is able to compensate for the faulty valves.

In patients with valvular disease the myocardium and the coronary arteries are likely to participate in the damage that has affected the valves, and share in the causation of heart failure. Various disturbances of the heart may therefore occur when valvular disease is present, and these disturbances rather than those of the valves should serve as an indication for the use of the drug. This is the attitude expressed by all students of the drug who have considered this matter, but it has not been discussed in the recent literature, because no doubt it has appeared self-evident.

One possible benefit of digitalis in valvular heart disease has, however, been recently suggested by Cohn and Fraser (22). They point out that a delay in the conduction of the cardiac impulse from auricles to ventricles may be of advantage to the heart when mitral stenosis is present, as such an effect would increase the time available for the left auricle to empty itself before the onset of ventricular contraction. They suggest that the action of digitalis in bringing about this delay of conduction may be a factor in its beneficial effect in cases of mitral stenosis, and that by the proper regulation of dosage, the conduction time may be constantly lengthened. No observations bearing directly on this suggestion have as yet appeared.

One form of valvular disease, aortic regurgitation, has gained the reputation of being a contraindication for digitalis. This tradition no doubt goes back to the original description of the lesion by Corrigan (27) in 1832, for there he says that digitalis lengthens diastole and so allows more blood to regurgitate through the incompetent valve. All of his patients with this lesion who received the drug seemed to have become worse from its action. Corrigan does not state, however, that the heart rate can be slowed by digitalis. Christian (16) has commented on this subject and says:

> There still lingers the tradition that aortic insufficiency contraindicates digitalis, because digitalis would prolong diastole and the large regurgitant flow of the blood under these conditions would stop the heart in diastolic paralysis; a good enough theory; only it seems to have no basis in fact.

Pratt (121) also states that this lesion is not a contraindication for the use of digitalis, and this has been the general experience of all who have paid particular attention to this subject.

It may be said therefore that in determining the indications for the use of digitalis, valvular lesions as such should be ignored, and other evidences of cardiac disorder should always serve as the guides for the use of digitalis in valvular heart disease. However, the suggestion of Cohn and Fraser (22) concerning the possible value of the drug in mitral stenosis is worthy of consideration and careful study.

5. Disturbances of the nervous mechanism

Certain disorders of the heart are encountered in which without any disturbance of the cardiac mechanism, the heart assumes an abnormally rapid rate. The underlying cause of these disorders is not well understood, but the more prominent symptoms seem to be dependent upon a functional derangement of the nervous mechanism controlling the heart, and are perhaps caused by an overbalancing of the inhibitory nerves, the vagi, by the accelerators. Two examples of such disorders seem worthy of consideration: the so called effort syndrome or neuro-circulatory asthenia, and hyper-throidism, since digitalis has been employed in the hope of lessening the tachycardia in each instance.

a. The effort syndrome is a condition which has come into prominence during the years of the recent war. It seems to be particularly prone to occur in young men of military age under emotional stress and strain incident to war, and affects probably those whose nervous make-up renders them predisposed. The chief symptoms consist of palpitation of the heart with tachycardia, breathlessness and cardiac pain on exertion, and manifestations of a disturbed nervous system, such as headache, giddiness and disturbed sleep. The symptom complex serves as a good example of what is generally called a cardiac neurosis, and because the more prominent symptoms are referable to the heart, digitalis has been used, especially with the idea of overcoming the tachycardia. Parkinson (119) has reported a study of the effects of digitalis on these cases carried on at the English Heart Hospital at Colchester, which was under the direction of Sir Thomas Lewis. Parkinson's results and conclusions serve as an example of the general experience with the use of digitalis in this condition. He administered full doses of the drug to a series of 20 patients. The heart rate was reduced but little, and the increase of rate which occurred with exercise or with standing was not controlled, to any appreciable extent, by digitalis. There was no effect on either the systolic or diastolic blood pressure. Parkinson states that digitalis scarcely influences this group of patients, even when the pulse is rapid, and he concludes that it is not indicated in the condition known as effort syndrome or neuro-circulatory asthenia.

b. Hyperthyroidism or exophthalmic goitre serves as another example of tachycardia which is primarily independent of any anatomical lesion of the heart or of any alteration in the mechanism of the heart beat. Several possible causes present themselves. The toxic substance generated by the thyroid gland may act directly on the heart or its nervous mechanism, producing the characteristic acceleration of rate; or there may be some fundamental change in the nervous system which manifests itself in part by causing tachycardia; or the increased cardiac rate may be secondary to the generalized increase in metabolic processes of the body. Without a better understanding of this subject, no rational therapy directed at the heart alone can be devised. Digitalis has been used with the hope of slowing the heart rate; but, as Cohn (20), Fulton (56) and others have pointed out, always without success.

It may be said that not only in the two examples of cardiac neuroses that have been considered, but in all types of disturbances of the nervous mechanism, digitalis fails to produce any beneficial effects. The tachycardia, usually the most prominent symptom, is not influenced by the drug. Whenever the diagnosis can be established with certainty, if should be considered unwise to use digitalis in the cardiac neuroses with any expectation of obtaining beneficial results.

X. DIGITALIS IN INFECTIOUS DISEASES

1. Fever in relation to the action of digitalis

During the course of severe infections, the possibility of heart failure is naturally constantly before the physician. Digitalis has been used both as a preventive measure with the idea of "supporting" the heart through a period of unusual strain and also as a curative measure when signs of heart failure have appeared as a complication of an infectious disease. In this connection, the relation of fever to the action of the drug has been a matter of discussion. Cohn and Jamieson (24) have reviewed this subject and state that definite differences of opinion exist among American, English and German clinicians. Some consider the drug is without power in the presence of fever; while it has been used extensively by others, especially in pneumonia. Mackenzie (109) states that digitalis has little effect upon the heart rate when it is elevated by agents which increase its excitability, and cites the effect of fever as an example. Cushny (30) also says that digitalis is especially apt to be inefficient when fever is present.

Cloetta (19), however, has recently recommended the use of digitalis in acute infections, combined with camphor and believes that it is important to begin the administration early in the course of acute infections. His recommendations are apparently based on somewhat empirical reasons however.

The relation of the body temperature to the action of digitalis has been subjected to animal experimentation. According to Jamieson (83), Gunn studied the effect of strophanthin on the perfused heart at temperatures ranging from 28° to 41°C. and found that the drug acted more quickly at higher temperatures. Recently Hirschfelder,

Bicek, Kucera and Hanson (81) have studied the effect of high temperature on the action and toxicity of digitalis. They injected the tincture intravenously into cats, the body temperatures of which were elevated by immersion in water, heated to from 43° to 46°C. They found that digitalis produced effects in these animals similar to those observed in normal animals, but there was a decided influence on the minimal lethal dose per kilo of body weight which is shown in the following table.

TEMPERATURE	AVERAGE LETHAL DOSE
°C.	*cc. per kilogram*
37–39	0.94
41	0.78
42	0.59
43	0.375

On the basis of these results Hirschfelder and his collaborators warn against giving large doses of the drug to patients with high temperatures.

2. Pneumonia

Pneumonia is the infectious disease in which digitalis has been most extensively used, and in which its action has been especially studied. These studies furnish valuable information regarding the action of digitalis in the presence of fever.

Fulton (56) in 1914 expressed the general opinion prevalent at that time regarding the employment of the drug in pneumonia.

> Where there is cyanosis with low blood pressure and a rapid, feeble pulse, the question always arises whether digitalis should be administered. The evidence in regard to its value in such cases is not satisfactory. It is not likely to do harm unless there is some involvement which might encourage the formation of heart-block, in which instance it should not be used.

Since this time, Cohn and Jamieson (24) have carried out a systematic study of the action of the drug in pneumonia, and have obtained results that give definite answers to the questions involved. They studied a series of 105 cases of pneumonia, 49 of which received digitalis, while 56 cases served as controls and were studied with

equal care. Electrocardiograms were obtained at frequent intervals, and particular attention was paid to the length of the conduction time, variations in the T wave of the electrocardiogram and the ventricular rate in cases of auricular fibrillation.

Digitalis was given by mouth in the form of digipuratum. They state:

> In general the criteria we employed permitted us to judge satisfactorily whether digiatlis was acting. We found that the signs appeared after the same amount had been given and following the same length of time in which these signs appeared in non-febrile cases originally studied. When no digitalis was given the signs did not appear.

Cohn and Jamieson conclude that digitalis acts during the febrile period, and produces a beneficial, possibly a life-saving effect when auricular fibrillation or flutter occurs during the course of pneumonia. Whatever beneficial action digitalis has on the function of the normally beating non-febrile heart may be expected from its use in the febrile heart in pneumonia.

Cohn (21) observed auricular fibrillation or flutter in 12 out of 123 cases of pneumonia; or in practically 10 per cent. He considers the frequency of these cardiac derangements in pneumonia sufficient ground for keeping patients under the influence of digitalis during the course of this disease. The drug was consequently routinely administered to pneumonia patients according to the following plan, the dose being indicated in grams of the leaf.

	DAY OF DISEASE								
	1	2	3	4	5	6	7	8	9
If seen early	0.5	0.5			0.5	0.5			
If seen late				1.0		0.5	0.5		

Stone, Phillips and Bliss (146) studied the effect of digitalis in a large series of cases of pneumonia in an army hospital during the recent war. They attempted to digitalize thoroughly the cases during the first forty-eight hours in the hospital by administering 0.17 cc. of a standardized tincture per pound of body weight in several large doses. The total amounts ranged from 20 to 30 cc.

With these doses vomiting occurred in only 4 to 5 cases; partial heart-block appeared in one, and there was a considerable rise of blood pressure in another. There were 871 cases in their series and the administration of the drug was begun at a certain date after about half the number of cases had been seen. The conditions under which these patients were observed did not allow detailed study but there was a striking difference in the death rate after the use of digitalis was begun. This is shown in the following table:

	BEFORE THE USE OF DIGITALIS	AFTER THE USE OF DIGITALIS
	per cent	*per cent*
Deaths not associated with sepsis	25.8	11.8
Deaths from uncomplicated pneumonia	17.1	11.2
Deaths from pneumonia complicating measles	46.3	14.8

Stone and his co-workers believe the tincture of digitalis was responsible for the decrease in the percentage of deaths in the cases not associated with empyema or other "septic" conditions, being definitely valuable in the type of cases whose deaths are associated with cardiac failure.

Caution must be exercised in drawing sweeping conclusions from this study, as under the circumstances, it cannot take into account certain possibilities such as variations in the virulence of the infecting organisms or other conditions altering the severity of the infections.

Jamieson (83) carried out an investigation on the action of the lethal dose of strophanthin in normal animals and in animals with experimental pneumonia. Cats and dogs were used and strophanthin was given by intravenous injections. Pneumonia was produced by intratracheal insufflation. Jamieson studied the effect of strophanthin in 21 cats that were not given pneumonia and 12 animals were studied that had pneumonia but were not given strophanthin. The action of the drug was studied in a large series of infected animals. The results of these experiments led to the following conclusions:

1. When a like amount of strophanthin is injected intravenously, the mortality is the same in both normal cats and in cats suffering from experimental pneumonia.

2. The minimal lethal dose is the same in normal dogs and in dogs suffering from experimental pneumonia.

3. The presence of an acute infection in these animals does not interfere with the action of strophanthin on the heart.

4. Electrocardiographic changes occurring in the heart's action when strophanthin is injected are found to be similar in normal and in infected animals.

5. The identity of strophanthin action in infected and in normal animals renders it probable that a like similarity may be anticipated in man, under normal conditions and in pneumonia.

This work corroborates the idea expressed by Cohn and Jamieson that the action of digitalis is the same in pneumonia as it is under non-febrile conditions. Probably the unfavorable influence of fever on the action of digitalis arose from the observations that the drug failed to slow the heart in febrile conditions, but it is now known that the drug usually fails to slow the normally beating heart when fever is not present except under special and rare conditions. Further work is necessary to substantiate the idea that digitalis "supports" the heart during pneumonia, although the work of Stone, Phillips and Bliss is suggestive and Cohn considers it desirable to give the drug to patients with the disease in anticipation of auricular fibrillation. The question may be raised, however, as to whether such use of digitalis may not tend to bring on auricular fibrillation in these cases.

3. Diphtheria

Diphtheria is another infection which deserves special consideration because of the frequency of cardiac damage as one of its most severe complications. The view has been held for a long time that the drug does not benefit the cardiac disorders following diphtheria and is possibly harmful in this condition. Only recently, however, has this matter been subjected to careful study by modern methods. McCulloch (111) after an extensive study of the heart in diphtheria by means of the electrocardiograph, and after many careful observations on the effect of digitalis in children, has drawn attention to the close similarity between the cardiac disturbances produced by diphtheria and the toxic effects of digitalis on the heart. In diph-

theria presumably through the action of the toxin on the heart, conduction is often damaged, premature contractions frequently occur, or there may be striking changes in rate, either a high grade of tachycardia or marked slowing. McCulloch attributes the slowing of the heart in diphtheria to vagus stimulation, and he has studied the effect which atropin has upon it. This interpretation is perhaps open to question. There is, however, such a close resemblance between the effects on the heart of diphtheria toxin and of digitalis that it seems to be adding insult to injury to administer the drug to patients with the cardiac complications of diphtheria. McCulloch's paper is a valuable contribution to the knowledge of indications for the use of digitalis.

XI. DOSAGE OF DIGITALIS

1. Oral administration

a. The amount of the drug. Withering laid down a sound principle for determining the proper dosage of digitalis when he wrote, "Let the medicine be continued until it either acts on the kidneys, the stomach, the pulse or the bowels; let it be stopped upon the first appearance of any one of these effects." He recognized the necessity of regulating the dose of the drug by its action, rather than by accepting a standard dose as applicable for various samples of the drug and for various types of disease in which it might be employed. In spite of his directions, standards of dosage of wide variations have been advocated.

Eggleston (42) states that the doses of the tincture of digitalis recommended by recognized authorities range from 2 minims (less than $\frac{1}{4}$ gram of the leaf) three times a day to 30 minims (3 grains of the leaf) three times a day; the larger dose being fifteen times as great as the smaller. Hatcher and Bailey (72) have discussed the use of the tincture of strophanthus and strophanthin, and have drawn attention to the great diversity of opinion regarding the dosage of these drugs, and to the apparent confusion relative to the activity of various preparations. It seems probable that variability of absorption is largely responsible for the lack of uniformity of dosage, as will be brought out later. It is apparent that many misconceptions have existed regarding the dosage of digitalis and its allies.

There has been recently a tendency to attribute poor results of digitalis to its use in inadequate doses.

During the past few years considerable attention has been focused on the matter of dosage, and much progress has been made towards establishing sound principles, based on accurate determinations in the laboratory and in the clinic. Eggleston and Hatcher deserve a large share of the credit for this progress, and their contributions to various phases of the subject have proved of much value.

The fundamental problem involved in the dosage of digitalis is the determination of the average amount of standard preparations required to produce maximum therapeutic results in the types of patients to whom the drug is usually given and which does not produce severe toxic symptoms. The method that has recently come into use is essentially the same in principle as that advocated by Withering, and consists in the administration of the drug to series of patients until well defined evidence of digitalis action appears. Modern methods, however, allow the detection of specific effects of the drug with greater precision and at an earlier stage than was possible in Withering's day.

After the determination of the average amount of the drug necessary to produce the desired effects in a series of patients, attempts have been made to convert this finding into a rule designed to allow others to employ the drug in the amount most likely to benefit similar patients, and to allow its use under conditions which do not permit the determination of the early evidences of its toxic action.

Following such carefully conducted studies as those of Mackenzie (109), recommendations as to dosage were made which reflected the results obtained in each series of patients. All of the students who employed accurate methods for the detection of digitalis action advocated larger doses than had been previously customary, but the earlier students of the present period of accurate objective clinical observation pointed out the fact that the dose must not only be fairly large but also that the drug must be continuously administered until definite effects were produced, when it should be either discontinued or much reduced in amount.

The study of Eggleston (42) marks the beginning of much progress in digitalis dosage. His paper published in 1915 brought out a

number of points of permanent value, and is an excellent example of clinical observation based on a sound training in the pharmacological laboratory. Eggleston undertook to determine whether or not it was possible to establish the dose of digitalis for man on the basis of the activity of the drug as determined by a biological assay. He studied, at the same time, several other problems directly concerned in the question of the dosage of digitalis and its allies and pure principles. These problems were:

1. The rate, degree and uniformity of the absorption of the crude drug and its active principles.
2. The influence of sex, age and weight on the dose.
3. The influence of the preparation-infusion, tincture, etc., on the dose.
4. The influence of the cardiac condition.
5. The influence of the size of the daily dose on the total dose required.

Eggleston used tinctures and infusions of digitalis, made from leaves of different sources and varying in activity, and crystalline digitoxin dissolved in 70 per cent alcohol or made into tablet triturates. The activity of each preparation was determined in terms of cat units by the method of Hatcher and Brody (74). These drugs were administered by mouth to a series of patients, some of whom had auricular fibrillation. Care was taken that none of the patients had received any one of the digitalis group of drugs within a period of not less than three weeks prior to the beginning of the observation. The patients were kept under observation in bed for from three to seven days before digitalis or digitoxin was given, whenever their condition justified such a period without medication. Body weight, intake and output of fluids, blood pressure, polygraphic—and in some instances—electrocardiographic records were obtained as indicated, as well as frequent physical examinations. Personal bias was, as far as possible, eliminated in judging changes in the condition of the patients.

The study was carried out on 47 patients, 6 of whom had two courses of treatment, making 53 in all. Fifteen studies were made on cases with auricular fibrillation and 38 on non-fibrillation cases.

The action of digitalis was determined by subjective and objective improvement in the symptoms and signs of heart failure and in the appearance of minor toxic effects. The phenomena included in this latter category were marked sinus arrhythmia, partial heart-block, premature contractions, nausea and vomiting.

The details of the method used by Eggleston are given because his work is a good example of the methods of clinical studies which have yielded valuable results, and indicate the various procedures necessary to prevent faulty observation and false conclusions when studying the effect of these drugs on patients.

The most important feature of Eggleston's study is that it enabled him to determine the amounts of the drugs in terms of cat units per pound of body weight required to produce therapeutic and toxic effects. In other words, he introduced two quantitative factors into the consideration of dosage that had previously received only indefinite consideration, and had not been brought into accurate relation with each other. Eggleston brought to the problem of dosage drugs of known activity and measured their effects in terms of the total amount used in relation to the weight of the individuals receiving them.

No definite difference was found between the amounts of the drugs necessary to produce comparable therapeutic or minor toxic effects in cases with auricular fibrillation and in non-fibrillation cases.

Eggleston draws the following conclusions and deductions from his studies:

1. The cat method of standardization of digitalis yields results on which the dose for man can be based.

2. The average therapeutic dose of digitalis given orally to man in the form of tincture is 0.146 cc. of an average high grade tincture per pound of body weight as established by thirty-three observations.

3. Fifteen observations have established 0.066 cat unit, or 0.023 mgm., per pound as the average therapeutic dose of crystalline digitoxin.

4. Approximately half of a total of 48 courses of administration of either digitalis or digitoxin, full therapeutic effects were secured with doses falling within 15 per cent above or below the average dose.

5. Doses considerably larger than the average were taken in 17 instances without the production of more than mild toxic symptoms.

6. The activity of the preparation of digitalis has no material influence on the dose required in terms of cat units.

7. Age, sex and cardiac condition do not seem to influence the size of the dose required.

8. Both digitalis and digitoxin are probably rapidly and fairly uniformly absorbed from the alimentary canal of man, but digitalis is less completely absorbed than is digitoxin.

9. Strophanthus, the strophanthins, ouabain, true digitalin, and some other digitalis substances are poorly or irregularly absorbed when given by mouth to man or to the higher animals and are unsuited for therapeutic use in this way.

Eggleston has pointed out the practical application of his results. In dealing with the tincture of digitalis, the dose may be taken for convenience as 0.15 cat unit per pound of body weight when the tincture possesses a strength of 1 cc. to the cat unit. This has been found to be the average strength of high grade tinctures and represents 100 mgm. of the crude drug. This strength may be accepted as a basis for the calculation of the total amount probably necessary to produce the maximum therapeutic results. A patient weighing 150 pounds would therefore require 22.5 cc. of such a tincture. Eggleston states:

> On the basis of the patient's actual or estimated weight, the total amount which would probably be required should be calculated and this quantity could then be divided into single or daily doses according to the rapidity with which it was desired to induce the full therapeutic effects. If, after the total calculated amount had been taken, the patient failed to show the full therapeutic effect or some minor toxic action indicated that enough had been given, the administration should be continued in small repeated doses until one or the other of these evidences called for its withdrawal.
>
> In this way it is possible to give a third to half of the total calculated therapeutic dose at a single administration, to follow this in from four to six hours with a quarter to a third of the total dose, and to give the remainder in a few doses of smaller size at intervals of from four to six hours. By this plan of administration, the full effects can be secured in from twelve to thirty-six hours in the majority of cases.

The administration of half of the total dose may call for the giving of from 5 to 15 cc. of the tincture at once, and it might be feared that such a large dose might cause gastric irritation and nausea or vomiting. I have given such doses repeatedly since the completion of the greater portion of this work and have never seen the least disturbance of any kind arising as a consequence. This is due to the fact that the nausea and vomiting following the administration of the digitalis bodies is of central origin and results only after the absorption of a sufficient quantity of the drug into the circulation.

It should be reiterated in this place that the use of such large doses of either digitalis or digitoxin as are mentioned is not a safe procedure unless the patient can be under nearly constant observation and unless the effects of the treatment can be graphically recorded at frequent intervals. This practically limits such procedures to hospital practice and to those well versed in the significance of polygraphic and electrocardiographic records.

Certain precautions necessary in using digitoxin according to the calculations he describes are pointed out.

Eggleston (45) has recently published a brief description of his plan for administration of digitalis by the body-weight method, and has given simple formulas for the determination of the dose of the leaf, the tincture and the infusion when the weight of the patient and cat unit strength of the drug is known. The average relative strength of these forms of the drug have been found by Hatcher and Eggleston to be

100 mgm. of the leaf = 1 cat unit
1 cc. of the tincture = 1 cat unit
10 cc. of the infusion = 1 cat unit

When the activity of a particular specimen given is not known, it is safe to use these figures for purposes of calculation; but then only 75 per cent of the calculated dose should be given in order to allow for the possibility of excessive activity of the specimen.

He recommends differentiating urgent and non-urgent cases, and points out the importance of reducing the dose when any member of the digitalis group has been taken in the preceding ten days, particularly when evidences of partial digitalization are present. Eggleston also prescribed certain safeguards which should be carefully followed. The signs of minor digitalis intoxication, such as nausea

and vomiting, reduction of the heart rate below 60 per minute, and the appearance of frequent premature beats; of definite heart-block; of marked phasic arrhythmia, or of coupled rhythm are to be taken as indications for the cessation of further administration. By the Eggleston method the calculated total amount of the drug may be given to urgent cases in twenty-four or thirty-six hours. By giving an initial dose of the drug consisting of one-third to one-half of the total calculated amount, and then by giving smaller parts of it at six-hour intervals, over-dosage is prevented as digitalis action becomes evident in six hours when the drug is given by mouth.

Eggleston comments on this method of administration as follows:

> The employment of this method of administration of digitalis is without danger to the patient if the directions are followed in detail and if the safeguards are carefully observed. By its employment it is usually possible to produce maximal digitalis action in from twelve to eighteen hours, and marked therapeutic effects are frequently observed within six hours after the initial dose. By its use, it is possible to dispense with the intravenous or intramuscular administration of ouabain, amorphous strophanthin, or other digitalis body in the great majority of cases of heart failure.

The demonstration of the necessity for using digitalis and its allies according to its activity as determined by biological assay is one of the most important results of Eggleston's work, and for that reason, the question of biological assay was taken up quite fully in the earlier part of the review. The relative strength of the various members of the digitalis group were also taken up, and the figures given in that portion of the review may be taken for the determination of dosage for their oral administration. However, the problem of absorption from the gastro-intestinal tract must always be borne in mind, and it will be brought out presently that this has a striking influence on the action of various drugs and preparations when administered orally.

Emphasis should be given to the work of Hatcher (68) on the persistence of the action of the digitalins in connection with dosage. He showed by animal experiments that all the digitalis bodies are synergistic and that the action of one is added to that of another. For this reason, the effect of any drug of this group contraindicates

the administration of any other of the digitalis bodies. Warning is gravely expressed by Cohn (21) that

> digitalis should, under no circumstances, be given to a patient who has previously been given digitalis in any form or by any route. The failure to obey this warning has, on many occasions, been followed by disastrous results to the patient.

The actual amount of digitalis in terms of the powdered leaf which is usually required to produce the maximum therapeutic results for an average adult weighing about 150 pounds is, according to Eggleston's calculations, 2.25 grams. Mackenzie (109) states that 5 to 8 drachms of the tincture usually produces the desired effects in his cases, an amount which should equal 2 to 3.2 grams of the crude drug. Cohn (20) found that slowing of the heart rate in cases of auricular fibrillation occurred after from 2 to 2.8 grams of the leaf had been given, and Cohn and Fraser (22) found that when the digitalis was administered as the tincture or as digipuratum, a disturbance of the rhythm was usually effected when an equivalent of from 2 to 4 grams of the leaves had been given, although symptoms of intoxication usually appeared before half of this quantity was given.

West and Pratt (156) using a dried aqueous extract of digitalis obtained satisfactory therapeutic effects with a preparation having a cat unit strength of 0.1 gram when from 1.4 to 2.2 grams had been given, while Cohn and Levy (25), obtained the desired therapeutic results when 1 gram of digipuratum of the same activity was given.

White and Morris (159) and Kay (88) have confirmed Eggleston's principles of dosage. Robinson (130) has also administered a standardized tincture in large single doses, calculated according to Eggleston's formula, to 100 cases of heart disease; the doses ranging, as a rule, from 15 to 25 cc. or 15 to 25 cat units, the amount being regulated by the body weight. He observed excellent therapeutic results without encountering any serious toxic effects. He found that the use of large single doses is apparently not dangerous under proper conditions of study, and brings the heart rapidly under the influence of the drug.

Pardee (118) has published the results of a study of sixteen patients to whom the tincture was administered. His results also closely

confirm the findings of Eggleston. He found wide variations similar to those seen by Eggleston which occur in the amount of the drug required by different individuals to produce the same effects, the variations in his series being from 36 per cent below to 50 per cent above average.

When digitalis is being administered in liquid form it should always be remembered that there is a great difference between the amount contained in a drop and in a minim. Cloetta (19), Pratt (121) Christian (16), Pardee (118), and others have referred to the inadequacy of dosage which has resulted from considering a drop equal to a minim, while in reality, according to Pratt, 1 cc. or 15 minims of the tincture contains 35 to 40 drops when the ordinary medicine dropper is used.

In summing up the work of these several students of digitalis dosage, it may be concluded that the average total amount of the drug necessary to produce therapeutic effects when administered orally has been firmly established, provided the activity of the preparation and the body weight of the patient are taken into consideration. This average total amount may be given in large single doses under proper conditions and when certain precautions are carefully followed, or it may be given in relatively small doses, at regular intervals provided doses are sufficiently large to allow the drug to accumulate in the body and are not below the rate of elimination of the drug, a matter to be considered later.

Pardee (118a) in his second paper on digitalis dosage expresses the opinion that when a tincture of unknown strength is being used, it is safe to follow the rule of giving 1 minim for each pound of body weight in a single dose when the effects of the drug are desired rapidly. This dose is well under the calculated maximun dose of Eggleston, and allows for a considerable increase in the strength of the tincture above that of the average preparation.

The question of applying the body-weight method to children has recently been investigated by McCulloch and Rupe (112). They observed the amounts of the tincture of digitalis necessary to produce definite effects in 36 children varying from one to fifteen years, none of whom had heart disease. Frequent electrocardiograms were obtained and the usual methods of clinical observation were carried

out. McCulloch and Rupe give the weight of the children in kilograms, but for purpose of comparison with the work already reviewed, it will be given here approximately in pounds, two pounds being allowed for each kilogram. The weights of the children ranged from 17 to 100 pounds.

The tincture employed was standardized at frequent intervals and had continuously a strength of approximately 1 cc. per cat unit. It was found to produce therapeutic effects in adults when given in doses of 0.15 cc. per pound of body weight. In normal children considering the group as a whole, from two to five times as much digitalis per pound of body weight was necessary to produce recognized digitalis effects as was found necessary to produce an optimum therapeutic effect in adult patients with heart disease. The difference of children in this regard was especially true for those weighing over 40 pounds. There were 12 such cases in the series, 8 of whom showed no response to doses of 0.29 to 0.48 cc. per pound, while the other 4 required from 0.62 to 0.87 per pound of body weight before showing evidence of the action of the drug.

Among the 24 children weighing less than 40 pounds, 14 responded to less than 0.5 cc. per pound while 8 required from 0.5 to 0.87 cc. per pound.

Two children aged twelve and twenty-one months respectively weighing 19 pounds each did not respond to the drug until 19.2 cc. had been given in 24 doses, requiring approximately 1 cc. per pound of body weight before showing evidence of digitalis action. The total amount of the tincture was given in this series in from 5 to 24 doses, being administered 4 times a day. Elimination therefore probably had little or no influence on the total amount taken, although of course absorption is a factor difficult to evaluate.

McCulloch and Rupe conclude that children weighing from 16 to 40 pounds, or up to about the age of four years, respond more readily as a rule to digitalis, than do those above this weight and age while the older children required a distinctly larger amount per unit of body weight than is required to produce comparable effects in adults with heart disease. Considerable variation in the amount of the tincture necessary to bring about a response in the hearts of the children was found, but it is evident that relatively large doses of digitalis

can be administered to children with comparative impunity. McCullock and Rupe (112a) have studied a second series composed of children with heart disease. In this series they found no qualitative difference in the effect of digitalis when compared to the action of the drug on adults. They found, however, that children with heart disease require about 50 per cent more of the drug per pound of body weight on an average than do adults to obtain the same results. Some of the cases required 100 per cent more of the drug, that is a quantity double the estimated dose, while others required only 10 per cent additional amount.

b. Absorption of digitalis from the alimentary tract is a problem which has an important bearing on the dosage of the drug when administered by mouth, and has recently received considerable attention. The relative rates of absorption of the various members of the digitalis group, variations in absorption of a single preparation and influences delaying absorption have been studied both in the laboratory and in the clinic.

Schmiedeberg (139) states that the active principles of digitalis, digitoxin, digitalin and digitalein are slowly absorbed from the gastrointestinal tract.

Ogawa (116) called attention to the delay in the time required for digitalis to affect the heart when given by mouth as compared with the time required after intravenous injection. He concluded that the slowness of absorption is the greatest factor in the "latent period" of digitalis action. He states that digitoxin is not absorbed from the stomach and only with relative slowness from the intestines. He found that by examining the withdrawn gastric contents that different preparations of digitalis have different rates of absorption, and that digitoxin for which he applied a colorimetric test, remains for a shorter period in the stomach when taken as digipuratum than when taken as powdered leaves or as the infusion.

Ogawa is of the opinion that the absorption of the digitalis bodies is further delayed by congestion of the abdominal vessels, as he found that experimental obstruction to the portal circulation prevented their absorption. Cloetta (19) also considers that congestion of the intestinal vessels and of the liver interferes with the absorption of digitalis. Eggleston (42) on the other hand, states that prompt and

efficient absorption of digitalis and digitoxin seems to take place even in the face of considerable abnormality of the alimentary canal, for patients manifesting evidence of marked congestion of this region, resulting even in repeated vomiting, respond quite as promptly and to the same doses as do those who are apparently free from disturbance.

Haskell, McCants and Gardner (66) studied the relative rate of absorption of various digitalis bodies from the gastro-intestinal tract of animals. They determined the amount of digitalis intravenously injected necessary to produce emesis after constant amounts had been given orally, and took as the measure of absorption from the gastro-intestinal trace the size of the intravenous dose necessary to produce this result, as the larger the amount absorbed from the gastro-intestinal tract, the less is needed by vein. They found that the tincture of digitalis was much better absorbed than the infusion, and that the expensive preparations, digipuratum, digalen and digipoten had no advantages over the tincture in regard to absorbability.

The most important work that has been done on the matter of absorption is that from the laboratory of Hatcher and from the clinic of Eggleston. Their numerous papers contain many references to this matter. Hatcher and Baily (61) called attention to the fact that the tincture of strophanthus is poorly absorbed from the gastro-intestinal tract, and Eggleston has recently stated in discussing the work of White, Balboni and Viko (158) which has already been referred to, that the tincture of squill owes its relative inactivity to its poor absorption. Hatcher and Bailey (73) have also pointed out that dangerous variations in absorption of strophanthus may take place. Eggleston (47) has recently summarized his ideas regarding the use of members of the group other than digitalis as follows:

> The materia medica of the digitalis group of drugs is large, but digitalis alone is well absorbed from the alimentary tract of man. Strophanthus, convallaria, squills, etc., are alike poorly absorbed and irregularly absorbed. Strophanthus deserves special mention, because it is 100 times as active as digitalis, yet the official dose is only half that of digitalis, and it is often given in equal doses. The irregularity of its absorption is of greater importance than the fact that its absorption is generally poor, for in some cases, serious poisoning has resulted from the rapid absorption of the customary dose. We are convinced that strophanthus should never be

used for oral administration to man on account of the danger of serious accident, despite the fact that it often has been so used with satisfactory results.

J. T. Halsey (62) has expressed similar views regarding the oral administration of strophanthus, and contends earnestly that the poor and irregular absorbability of strophanthus from the alimentary canal should prohibit its use by mouth.

Recent interest has centered largely on the absorbability of the tincture of digitalis, the most widely used form of the drug. Many references are found in the older literature regarding the slow absorption of the drug in any form, but the recent clinical studies furnish definite facts regarding the absorption of digitalis from the gastro-intestinal tract in man. Eggleston (47) states that the absorption of a single dose of a high grade tincture is apparently completed in six hours and he quotes the results of Pardee and of Levy, both of whom obtained electrocardiographic evidence of digitalis action in from two to four hours after the drug was given by mouth. Robinson (129) administered large single doses to 26 patients with auricular fibrillation and observed the onset of ventricular slowing constantly in from 2 to 5 hour after the administration of the drug. These findings indicate that with the tincture he used a fairly rapid and uniform rate of absorption took place from the alimentary tract.

Pardee (118a) has studied the rate of absorption of digitalis from the gastro-intestinal tract. He gave the drug in the form of the tincture in doses determined by allowing 1 minim for each pound of body weight, and administered this amount in a single dose. He then followed the action of the drug in frequently taken electrocardiograms, noting especially variations in the T wave and in the heart rate. Changes in the T waves indicative of digitalis action were observed within two hours of taking the drug in three of nine patients, while within three hours, these changes were observed in seven of the nine patients. Pardee's observations are confirmatory of those of Robinson, although the doses used by the former were considerably smaller. Pardee considers that the variation in the size of the dose within certain limits does not appear to have a marked influence on the time of onset of the digitalis action.

Eggleston (42), has compared the absorption of the tincture of digitalis with that of digitoxin, digitalin and digitalein. The last two substances are so poorly absorbed from the alimentary canal as to render them unsuitable for therapeutic use, while the absorption of digitoxin is slightly less rapid than that of the tincture.

Attention has been directed recently, however, to marked variations in dosage required to produce well defined digitalis action when tinctures carefully assayed by the cat method were used. Wedd (152) found that in one patient 100 cc. of a standardized tincture produced no effect while six months later definite digitalis action followed the administration of 35 cc. of another equally active tincture. Of the first tincture 280 cc. were given to another patient during a period of ten weeks and produced no clinical symptoms. He found that from 24 to 34 cc. of the first tincture were required to cause inversion of the T wave of the electrocardiogram while it occurred with 10 cc. or less of the second equally active tincture. Wedd attributes this difference in the action of the two tinctures to variations in absorption, and says that it is evident that biological standardization is no guarantee of the clinical efficiency of a given preparation of the drug.

A similar experience occurred to Oppenheimer (quoted by Eggleston (46)), who gave 5 to 9 times the usual dose of the tincture without evidences of either therapeutic or toxic action. Although individual susceptibility may play some rôle in producing these marked discrepancies, the variations in absorption seem to be the prime factor.

Hatcher (71) has taken cognizance of these variations in digitalis action, the frequency of which is not yet known, and has investigated them. He says that

> Certain of the digitalis principles are readily absorbable from the gastrointestinal tract of man, as well as that of animals, while others are absorbed much less readily, and it seems probable that the failures just mentioned arose from the fact that preparations contained relatively large proportions of the less readily absorbable active principles.

Hatcher has found that the more readily absorbable principles are soluble in chloroform, and he describes a method for separating the chloroform soluble from the chloroform-insoluble principles. He has

obtained a chloroform-soluble substance resembling somewhat digitoxin, both chemically and pharmacologically. It may be dissolved in alcohol and is miscible with water without precipitation. The resulting weak alcoholic solution has been found to undergo little change during a period of a year since it has been under observation. This preparation seems to exert the typical cardiac action of digitalis, and has all its other advantages.

The clinical use and especially the absorbability by patients of this preparation has been studied by Eggleston (46) who has published some preliminary observations. He shows the marked uniformity of absorption of the chloroform-soluble extract of digitalis prepared from a variety of different leaves. This uniformity contrasts sharply with the variations noted in the use of certain tinctures from a variety of sources.

> The chloroform-soluble extract is shown to be absorbed at least as rapidly as the best tincture of digitalis, and its persistence of action is apparently of the same order as that of digitalis of the best grade. The observations indicate that for oral administration the chloroform-soluble extract is not superior to a well absorbed tincture of digitalis, but it is far superior to tinctures which are derived from a variety of sources, the absorption of which shows very marked variations when individual specimens are compared. The chloroform-insoluble extract is very poorly absorbed from the human alimentary tract as well as from that of the cat.

It is evident that absorption must be taken into more strict account than it has been in the past in determining the efficiency of a digitalis preparation, and means must be devised if possible to determine its absorbability as well as its activity in the standardization of the digitalis intended for oral administration.

The effect of the gastro-intestinal secretions on the digitalis bodies is a problem closely allied to that of absorption. Ogawa (116) studied this problem in animals and in man, and found that strophanthin was destroyed by the gastric ferments, just as Holste (quoted by Ogawa) concluded that the pancreatic secretion destroyed digitalin. Ogawa's study revealed, however, that the glucosides of the digitoxin fraction are resistant for several hours to the juices of the gastro-intestinal tract.

Cloetta (19) has investigated the effect of gastric juice on digitalis in vitro, his digalen preparation being subjected to shaking for one hour at 38°C. with varying percentages of hydrochloric acid. The percentage of the drug destroyed was then determined and the following results were obtained:

with 22 per cent HCL	100 per cent digalen destroyed
with 12 per cent HCL	60 per cent digalen destroyed
with 4 per cent HCL	40 per cent digalen destroyed
with 3 per cent HCL	35 per cent digalen destroyed
with 2.5 per cent HCL	35 per cent digalen destroyed
with 1.5 per cent HCL	25 per cent digalen destroyed

Cloetta considers that a "nerve poison" is generated by the action of hydrochloric acid on digitalis, the therapeutic properties of which are destroyed. He recommends giving the drug when the stomach is empty, and giving it with an alkaline mineral water, weak tea or a mucilage. He also believes that his findings indicate the usefulness of giving digitalis by rectum, which he advocates. Further study of these subjects is needed before they can be adopted as principles influencing the therapeutic use of digitalis.

The problem of the decomposition of various digitalis bodies by acids and digestive ferments has been discussed by Hatcher and Eggleston (78) in their studies in elimination, and a review of a number of experimental studies of this subject is given, including that of Holste quoted by Ogawa. Following their analysis of these various investigations, they say that there is no convincing evidence that any of the digestive juices or their ferments have any important destructive action on any of the digitalis glucosides following their therapeutic administration by the mouth.

c. The speed of action or time elapsing between the oral administration of digitalis and the appearance of its effects is also a matter on which absorption has an important bearing. The fact that digitalis requires many hours or even days to affect the heart when given in the customary doses has been perhaps the chief disadvantage in the use of the drug in cases of heart disease in which prompt action is urgently indicated.

Cushny has stated that one great limitation in the use of digitalis is caused by the slowness with which its action is elicited. "Rarely

is any distinct change to be seen before the fourth day of treatment, and this precludes its use in the most acute cases." (Quoted by Eggleston (42)). Recent clinical studies have shown, however, that it is the size of the dose rather than the delay in the absorption or in the action of the digitalis that is the most important factor in regulating the speed of action of the drug. It is necessary for a certain amount of the drug to be present in the body before the action appears, and the action appears much more quickly with large than with small doses, several or many of which are needed to supply the amount of the drug necessary to exert its action. It has been the time required for the accumulation of a sufficient amount of digitalis that has become largely responsible for the ideas regarding the very slow speed at which the drug exerts its action.

Eggleston (42) has shown the relation between dosage and speed of action for digitalis and digitoxin, large doses of the digitalis bodies becoming active on an average in 13 hours; small doses in thirty-eight hours while large doses of digitoxin required fifteen hours to produce their earliest effect, and smaller doses required forty-two hours. He demonstrates that both these drugs when given in large doses can induce full therapeutic effects within comparatively few hours after the administration of the first dose.

Robinson (129) has investigated the question of the rapidity of the action of digitalis by giving the full calculated amount of the tincture in a single dose to patients with auricular fibrillation. In a series of patients in whom digitalis caused a striking reduction of the ventricular rate, he found that ventricular slowing (or disappearance of auricular flutter) began in from two to five hours in all of the 16 cases where the initial effect was observed, and that maximum slowing in 26 cases occurred in from six to twenty-six hours. As only one dose was given in most of these cases, the question of the accumulation of the drug played no part.

These results have been confirmed by Eggleston (46) and by Pardee (118a), who found that two or three hours after a single large dose of the tincture slight changes in the T wave of the electrocardiogram characteristic of digitalis action usually appeared. Eggleston also quotes Scott as having obtained digitalis effects in from one to two hours by the administration of 10 cc. of the chloroform-soluble extract of digitalis given in a single dose.

Cohn and Levy (25) have compared the speed of action of comparable doses of digitalis (digipuratum) when given by mouth and g-strophanthin when injected intravenously. An effect with digitalis has been observed in a little more than two hours, while the speed of action is often faster with strophanthin than with digitalis, though when strophanthin is given in divided doses it may require nearly two hours to obtain an effect. In other instances, an effect may be obtained, as is well known, in twenty minutes or less.

This matter of speed of action of digitalis has been recently summed up in a vigorous way by Hatcher (70).

> It is necessary to call attention again to the difference between an immediate action and immediate effect, because it has long been taught, without a particle of real evidence, that the action of digitalis cannot be induced promptly. The whole range of digitalis action up to the maximum, that is, cardiac stoppage, can be induced in from five to fifteen seconds by the intravenous injection of digitalis tincture deprived of its alcohol, or digitoxin. This simple experiment disposes forever of the mischievous claim that digitalis action is slow. The *effect* of therapeutic doses is *gradually* induced; the action is *immediate*. A bullet fired through the heart *acts* instantaneously; the *effect* is a fatal hemorrhage, the rapidity of which depends largely on the size of the wound. With suitable dosage, digitalis exerts its action in much less time than was formerly believed to be possible.

2. Intravenous administration

The value of the intravenous administration of ouabain, strophanthin, and some other principles of this group is generally recognized, and it is considered a life-saving measure because of the promptness with which the action of these drugs can be obtained in urgent cases of heart failure. In emergencies, however, the cause of heart failure may be difficult to determine and when it occurs under such conditions as during a surgical operation, its cause is often incorrectly attributed to "cardiac dilatation," as Levine has recently pointed out. The use of large doses of digitalis by mouth and the prompt action which usually results makes the use of these drugs by intravenous injections rarely necessary. It must always be employed with caution, as has been pointed out in discussing fatalities following its use, and intravenous injections should never be given to

patients who have been receiving full doses of the digitalis bodies in any form.

Digalen, the so called soluble digitoxin, prepared by Cloetta (17) is the first form of digitalis recommended for intravenous employment. Edens (36) was among the first to report favorable results with the intravenous administration of this drug, and he emphasizes especially the rapid action thus obtained, and the fact that the drug can be used in cases where absorption from the gastro-intestinal tract would probably be distinctly faulty. He considers its use not without danger, however, and recommends its use by slow injection in desperate cases. Cloetta (19) has recently expressed his belief in the intravenous use of digalen as the ideal method of giving digitalis.

Strophanthin was introduced as a drug for intravenous administration by Fraenkel, and its use is fully discussed by Fraenkel and Schwartz (54). They recommended a dose of 1 mgm. ($\frac{1}{6}\frac{1}{7}$ of a grain) but say it should not be given more often than once a day. Agassiz (2), studied the effect of intravenous injections of strophanthin on a series of cases of auricular fibrillation and recommends doses of $\frac{1}{2}\frac{1}{5}\frac{1}{0}$ to $\frac{1}{5}\frac{1}{0}\frac{1}{0}$ grain repeated several times every one to three hours for several doses. Ventricular slowing usually resulted from one injection. It may appear as early as half an hour after the injection, but the ventricular rate may continue to be further slowed during the following twenty-four hours. Two or three injections are usually sufficient to produce the normal ventricular rate in 4 to 9 hours. Strophanthin employed intravenously seemed to possess action quite similar to the other members of the digitalis series. Agassiz found the most suitable method of administration to consist in the injection of $\frac{1}{2}\frac{1}{5}\frac{1}{0}$ grain repeated after three hours, and followed after a further interval of three hours by an injection of $\frac{1}{5}\frac{1}{0}\frac{1}{0}$ grain if required. The injection may be followed by pain at the site of injection and by a rise of temperature. In one instance, a patient died unexpectedly some twelve hours after the injection had ceased, but the relation of cause and effect was not definitely established.

Fulton (156) reports a case of auricular fibrillation treated by intravenous strophanthin in which the pulse-rate fell from 144 to 34 within a period of about twenty-four hours, after two doses had been given, the first of $\frac{1}{2}\frac{1}{5}\frac{1}{0}$ of a grain and the second of $\frac{1}{1}\frac{1}{5}\frac{1}{0}$ of a grain.

The condition of the patient passed quickly from one of extreme discomfort with dyspnea and restlessness to a condition of perfect comfort.

Such observations as those of Agassiz and Fulton indicate that doses of 1 mgm. ($\frac{1}{60}$ grain) as advocated by Fraenkel are too large, and fatal accidents have resulted from the use of strophanthin in such doses, as has been brought out when digitalis fatalities were discussed. However, the work of Levine and Cunningham (94) indicates that it is no more dangerous than digitalis intravenously administered when the so-called margin of safety is considered, the average difference between the minimum lethal dose and the minimum toxic dose being 48 per cent in each instance. They have also found that various digitalis preparations act as quickly on the heart when injected into the veins as does strophanthin. They observed toxic effects two minutes after the intravenous injection of digitalis and cardiac standstill in sixteen minutes. All effects produced by either digitalis or strophanthin were seen to occur within six minutes after the injections.

Levine (92) has suggested a fractional method of intravenous injection of strophanthin on the basis of his experimental studies of the action of the drug on the living cat's heart. He points out that numerous fatalities have resulted from the intravenous administration of strophanthin, but most of them have occurred when the drug was given to patients who recently had taken digitalis, or when large doses were repeated on the same day. His experiments show that it is practically impossible to foretell the toxic dose for patients but they indicate that a "margin of safety" exists between the minimum lethal dose and the minimum toxic dose. Levine recommends that strophanthin be injected in several fractions of the desired dose, a half hour intervening between the fractions, during which time the signs of intoxication are watched for. This procedure will prevent giving more than one fraction, say 0.1 mgm. in excess of the amount necessary to produce the earliest toxic signs. Electrocardiograms are very useful in showing premature beats or changes in the P-R interval as a result of the drug. This procedure should certainly diminish or avoid the dangers of the drug. According to Levine, Vaquez and Lutembacher have reported almost 2000 intravenous injections of ouabain without harm or fatality.

Danielopolu (34a) has also recently stated that strophanthin can be safely given only in small doses, and recommends the use of 0.25 mgm. intravenously two or three times a day. This he calls the method of fractional doses, and says that by observing the patient carefully before each dose, the drug can be given to patients with extreme myocardial derangement or with kidney disease, which are to be taken as contraindications when larger doses are employed.

Cohn and Levy (25) report that the g-strophanthin which they have used in their comparison with digitalis had an average cat unit of 0.104 mgm. and was given usually in two doses at an interval of one hour—the first of from 0.4 to 0.5 mgm., and the second from 0.3 to 0.5 mgm. No serious untoward effects were observed after these doses.

The drug produced premature beats and ventricular ectopic tachycardia in 52 per cent of the cases of auricular fibrillation and 12.5 per cent of the cases with normal hearts. These toxic effects always appeared within twenty minutes after the injection causing them and disappeared within eight hours. Nausea and vomiting were noted in 10 per cent of the cases. Comparable doses of digitalis by mouth caused undesirable effects in a much smaller percentage.

An important indication for the intravenous use of a digitalis body is persistent vomiting which may be associated with heart-failure as, under such circumstances, it may be impossible to administer the drug orally. Under these circumstances, strophanthin had best be used, for although other digitalis bodies have been employed intravenously, they have not as yet been placed upon as sound a basis for this purpose as strophanthin.

3. Subcutaneous and intramuscular administration

Subcutaneous and intramuscular administration has not proved desirable, and it has not been employed in any of the recent studies of digitalis. Several preparations have been recommended as suitable for subcutaneous and especially intramuscular injections, but all are decidedly painful and apt to cause necrosis, and their dosage has not been accurately determined. Hatcher and Eggleston state emphatically as a conclusion from their studies on the absorption of drugs in general that no rule can be formulated for the calculation of the ap-

propriate dose by one mode of administration from the dose by any other mode of administration. Such determination can be made only be experiment.

4. Rectal administration

Rectal administration has been recommended by Eichhorst (49) in the treatment of chronic myocardial insufficiency. He described several cases which were not benefited by the usual drugs and which did not respond favorably to three powders a day composed of 0.1 gram of powdered digitalis, 1 gram of diuretin and 0.5 gram of saccharin. These cases showed beneficial results from small daily enemata containing 10 drops of digalen (Cloetta), 10 drops of the tincture of strophanthus, 0.3 gram of theocin and 5 cc. of lukewarm water. This prescription was injected daily into the bowel and retained. Eichhorst has continued their use over periods of years without difficulty. Five to ten drops of the tincture of opium is added when there is pain or difficulty in retaining the enemata. Eichhorst states that very striking results were obtained by the use of such enemata.

Cloetta (19), has commented upon Eichhorst's results, and he is favorably disposed toward the method. He believes that one advantage of rectal administration is that it does not subject the drug to the action of the gastric juice, which his experiments indicate may destroy it. He believes the favorable results that have been reported are accounted for also by the fact that some of the veins leading from the rectum, the inferior and part of the middle hemorrhoidal veins, empty directly into the inferior vena cava, and do not send the blood through the liver. Because of this, some of the drug introduced into the rectum would probably reach the heart without going through the liver, where it may be destroyed.

The rectal administration has not been extensively used, but it deserves further study, and more should be known regarding the action of the digitalis bodies when introduced into the body by this route.

XII. PERSISTENCE OF ACTION

It has long been known that the action of digitalis persists after the drug is discontinued. Withering (163) recognized this fact in regard to nausea and vomiting, and recommended that the drug be stopped as soon as its activity became manifest, inferring that its beneficial effects persist thereafter. A number of problems are involved in the persistence of action of digitalis. Absorption, fixation by the tissues and especially the destruction or elimination of the drug from the body, may all play some part in determining the continued action of the drug, and as there is but little known regarding any of these matters, no satisfactory explanation of the fundamental problem can be offered.

A number of clinical observations have been made with exact objective methods which show the length of time patients remain under the influence of the drug after full digitalization has been accomplished and the drug withdrawn. Bastedo (5) observed the continuation of digitalis heart-block for three and a half weeks after the withdrawal of the drug. Cohn (20) found by means of electrocardiograms that delayed conduction always persisted for two days in relatively healthy hearts and exceptionally for two weeks after the discontinuance of digitalis, while Cohn, Fraser and Jamieson (23) observed the persistence of the T wave changes in the electrocardiogram for from five to twenty-two days after the drug was stopped.

Eggleston (39) has studied the relative duration of various cardiac manifestations of digitalis action in fifteen cases of his own and from the literature. Coupled beats persisted from four to twelve days, heart block three to six days, combined phenomena six days, auricular fibrillation three days, extrasystoles and sinus arrhythmia two days. Conclusions regarding the relation of digitalis and the disappearance of transient auricular fibrillation is hardly justified.

Robinson (129) followed the ventricular rate of a number of cases of auricular fibrillation after it has been slowed by large single doses of the tincture of digitalis. In twelve cases which were carefully controlled, the ventricular rate began to accelerate in from four to fifteen days after the administration of the dose of digitalis which had caused marked slowing. This acceleration was taken as evidence

that the heart had ceased to be under the action of the drug. The drug was active on an average, for nine days and six hours in these cases. Kay (88) has reported ventricular slowing in auricular fibrillation for from three to five days after doses of digitalis given by the "Eggleston method."

It is evident that various manifestations of digitalis action persist after the drug is withdrawn for from two to twelve days in most cases, but may persist for three weeks or more.

The action of strophanthin when administered by vein has been found by Agassiz (2) to retard the rate of the ventricles of cases of auricular fibrillation for two or three days, when acceleration begins, and the original rate, present before treatment, is seen again in about one week.

Cohn and Levy (25) have compared the persistence of action of digitalis (digipuratum) and g-strophanthin given in comparable doses to cases of auricular fibrillation and found that while the digitalis effect endures usually beyond ten days, and has lasted as long as twenty-three days, it is rare for strophanthin to keep the ventricular rate low for more than five days. It did so once for nine days, however.

A question closely allied with the persistence of action is the so called *cumulative action* of digitalis. Eggleston (39) has discussed the term "cumulative," which is a very loose one. It is generally taken to express the development of signs of action during the administration of small repeated doses of a drug which are much more marked than those caused by a single small dose. Toxic symptoms are usually implied. Accepting this definition, the cumulative action in the case of digitalis is simply the result of a summation of amounts absorbed and active in the body when the intake of the drug is greater than its elimination. The continued use of small doses of the drug raises by the process of summation the total amount of the drug active in the body, and perhaps fixed by the heart or the nervous tissues, to such a point that toxic symptoms develop. When the persistence of action of digitalis is borne in mind the fear of its so called cumulative action can be put aside.

Hatcher (68) has investigated the persistence of the digitalins by means of animal experiments, especially with the hope of throwing

some light on the cumulative action of the drug, which generally means, he says, action which is manifested rather suddenly after the continued use of doses which singly do not cause perceptible effects. The method he employed was as follows: The fatal dose of the digitalis body for a given species was determined in a series of experiments. After toxic, but sublethal doses of the drug had been given, the animals were kept under observation for periods of one to thirty days, and then the percentage of the standard fatal dose required to kill in a characteristic way was determined. The decrease in the amount necessary to produce a fatal result was taken to represent the amount of the drug remaining in the body of the animal. Hatcher and Brody (74) had previously shown that the various digitalis bodies are synergistic, and that ouabain was capable of replacing the various digitalins in the estimation of the fatal dose, and this drug was generally employed for the second injection. Cats were found to be the most useful laboratory animal for this purpose. The many experiments will not be reviewed. Certain conclusions are of importance from the point of view of the therapeutic use of digitalis. Hatcher says that the production of the phenomena commonly called "cumulative action" of the digatalins depends on the relationships existing among a number of factors, including absorption, elimination, and persistence of action, all of which are in need of investigation. The use of the term cumulation tends to perpetuate a misconception. The action of the digitalis persists for periods of time which vary widely with different members of the group, the action of digitalis and digitoxin persisting much longer than those of the other digitalins in common use. The cardiac action of a single very large intravenous dose of digitalis or digitoxin may persist for a full month in the cat, while similar doses of digitalin, ouabain or strophanthus persist for only a day or at most a few days.

Careful regulation of the therapeutic dosage of the digitalins is necessary in order to avoid accidents. This is especially necessary when they are used in such a way that the action is elicited promptly during the period when the action of a previously used digitalin persists, and in this connection it must be remembered that every digitalin is a synergist of every other member of the group.

XIII. ELIMINATION OF DIGITALIS

Little is known and relatively little has been thought apparently regarding the matter of the ultimate fate of digitalis in the body, its destruction and its elimination. It is a matter of real importance, however, in the therapeutic employment of digitalis, when frequent doses of the drug are being given, and especially when it is desirable to keep a patient constantly under the influence of the drug without producing toxic symptoms. This is apparent from the foregoing discussion of the "cumulative action" of the drugs of the digitalis group.

Schmoll (141) recommends that 0.1 gram of digitalis be given daily to heart cases in order to take advantage of what he calls the tonic use of the drug, and he says this dose causes no toxic effects because it is the amount of the drug which can be excreted daily.

The rate of disappearance from the body has been the subject of a clinical investigation by Pardee (118). He points out that when digitalis is given for the purpose of keeping a patient constantly under its influence, improper dosage makes the patient liable to pass gradually out from under the influence when too small a dose is given, or with over-administration, leads to toxic symptoms. As animal experiments cannot give a definite answer as to the rate of disappearance of the drug from the human body, Pardee investigated the question directly in patients by the following method. The tincture of digitalis was given until mild toxic symptoms appeared, when it was stopped entirely for a number of days. It was then given again until the same toxic symptoms reappeared. The difference between the amount of the drug used in the second and in the first course, divided by the number of days between the two toxic points, is taken to indicate the daily average amount of the drug that had disappeared from the body in the interval. It is assumed that there is no change in the patient's tolerance for the drug, a fair assumption in the light of the results with repeated courses in the same patients. The initial doses were so arranged that toxic symptoms appeared in from two to six or eight days; while the second course was usually complete in an average of five days, although it was sometimes prolonged.

Vomiting was the usual toxic symptom employed. Twenty-two tests were carried out on 16 cases, all of whom had a rather marked degree of heart failure before the initial course, but were in better condition when the second course was given. A standardized tincture having a strength of 1.25 cc. per cat unit was used.

The method employed by Pardee showed an average daily rate of disappearance of the drug from the body of 22 minims of the tincture. In half the cases the amount was below and in half above the average, the maximum variations being from 55 per cent below to 82 per cent above. The results of this investigation resemble other work on digitalis in the variability of figures, but in 18 of the 22 tests, the results lay between 12.3 and 30.6 minims per day; while in eleven tests, half of the total, it was between 13.3 and 27 minims, the latter a total variation of only 62 per cent. Pardee says:

> It is evident from this that the average figure of 22 minims per day would afford a fairly satisfactory basis for long continued digitalis medication, since in only half of the cases would it be much more or much less than the patient's ability to dispose of the drug. These results demonstrate the reason for the approximate efficiency of a dose of ten minims of the tincture twice a day, which has commonly been considered sufficient to maintain constantly the digitalis effect. They also demonstrate a new phase of the variability from one individual to another, in the action of digitalis, a variability in the rate of disappearance from the body.

It is interesting that Schmoll's figure of 0.1 gram of digitalis which is equal to about 15 minims of the tincture recommended a number of years ago, should approximate Pardee's figure fairly closely. The importance of this subject warrants its further clinical investigation.

Hatcher and Eggleston (78) have recently published extensive studies in the elimination of certain of the digitalis bodies from the animal organism. Their review of the literature shows that the subject is in an unsatisfactory state. Their studies deal mostly with the elimination of various pure digitalis bodies in the rat, while the elimination of ouabain in the cat and dog was also investigated.

Ouabain disappears rapidly from the blood following injection, and seems to be taken up by the liver where it is apparently decomposed.

Both destruction in the body and elimination by the kidneys probably occur. Many points regarding the elimination of the digitalis bodies remain to be settled, and this work of Hatcher and Eggleston does not appear to present any facts which can be applied directly to the therapeutic use of digitalis.

XIV. PREPARATIONS OF DIGITALIS AND ITS ALLIES

The number of digitalis preparations is very great and they have been shown to vary greatly in activity. It is hardly worth while to attempt a description and criticism of the many proprietary preparations. It seems more desirable to attempt to review the rules by which the useful preparations can be distinguished from the less valuable. Of course activity as established by a reliable form of biological assay, preferably the cat method of Hatcher and Brody (74) is essential.

The cost and recently the availability, especially of foreign products are to be considered even when the medicinal qualities are satisfactory. As Eggleston (47) has recently stated:

> Of the many proprietary preparations and specialties which are offered with high claims for oral administration, none is superior to the powdered leaf or a tincture of high grade, and most are decidedly inferior. All are quite costly and the price of some is exorbitant. If one feels impelled to employ one of these, digipuratum or digipoten will be found to be the best, but these are merely carefully assayed, purified preparations from good digitalis leaves.

The dried aqueous extract recently described by West and Pratt (156) at first seemed to be an excellent preparation but has since proved too hydroscopic. It was used by them in capsules containing 0.1 gram. The chloroform-soluble extract which Hatcher (71) has obtained has been successfully employed by Eggleston (46), and may prove to be superior to the ordinary tincture, on account of its uniformity of absorption.

The infusion of digitalis has no advantage over the tincture or powdered leaves, and the large amount necessary for proper dosage make it less desirable.

Weiss and Hatcher (54a) have recently investigated the relative merits of the infusion and the tincture once more. They found that

the infusion of digitalis prepared according to the method prescribed in the United States Pharmacopoeia does not represent the drug completely, so that its strength cannot be determined from that of the leaf from which it was made. They give a method by which all water-soluble active principles can be obtained. They show that the full strength of the drug is represented by the tincture, and neither the infusion nor the tincture contain amounts of the saponin bodies sufficient to cause undesired effects. Weiss and Hatcher point out that they can find no evidence of any qualitative difference between the actions of the tincture and those of the infusion. The common belief that the infusion deteriorates rapidly is apparently much exaggerated, because Weiss and Hatcher report that an infusion prepared by the method they recommend, kept in hermetically sealed bottles for two years and five months retained its activity unimpaired, as shown by tests on cats and by its therapeutic results. A properly prepared and preserved infusion would seem therefore to have a usefulness quite similar to that of a good high grade tincture.

None of the preparations claiming to be devoid of effects on the gastro-intestinal tract should be used on that account. The absence of this effect must be viewed as evidence of inactivity, because of lack of potency or poor absorption, and if gastric symptoms are not produced, the desirable effects can not be expected.

Strophanthus and squills as well as most of the purer derivatives of digitalis are so poorly and irregularly absorbed from the gastro-intestinal tract that they should never be used for oral administration. Crystalline g-strophanthin is the most satisfactory drug for intravenous use provided it is protected against deterioration by regulation of its reaction and by its being marketed in hard glass containers. The importance of this has been shown by Levy and Cullen (95).

The French preparations, Arnaud's ouabain and Nativelle's crystallized digitaline have been assayed by Levine (93), using the cat method, and he found that this ouabain had a cat unit of 0.059 mgm. It is nearly twice as active as the ouabain used in America, which Hatcher has shown to have a constant unit of 0.1 mgm. Nativelle's crystalline digitalin in sterile oil capsules had a cat unit of 0.86 mgm., the tablets of 0.71 mgm. Levine suggests that the dose of 0.25 mgm. of digitalin advised by the manufacturers is too small

for good therapeutic effects. Perhaps the sterile oil preparation is the most satisfactory for intramuscular injection if such use of the drug be found necessary. It was stated, when the so called digitalis group of drugs was discussed as a whole, that this review would deal almost exclusively with digitalis and strophanthus. Recently three other members of the group, squill, apocynum and convallaria have been investigated from the point of view of their therapeutic effects by White and his collaborators. As their therapeutic value has been compared with that of digitalis, a brief statement may be made regarding their use in the treatment of heart disease. The digitalis-like action of squill was studied in fourteen patients by White, Balboni and Viko (158). Thirteen of their cases showed auricular fibrillation, most of which had been previously shown to respond well to digitalis. They found that ventricular slowing and the characteristic changes in electrocardiograms were produced by the drug, indicating that squill does have a definite digitalis-like action, but only when doses much larger than those usually recommended were given. They administered the tincture of squill, and found that from 8 to 16 cc. were necessary at each dose instead of the recommended dose of 1 cc. (15 minims). No definite diuretic effect could be attributed to the action of the drug. Eggleston, as previously mentioned, stated in discussing this paper that in his opinion the large doses were necessary on account of the poor absorption of the drug from the gastro-intestinal tract. He further says that he can see no reason for using squill in place of digitalis in the treatment of heart disease.

Apocynum and convallaria have been similarly studied by Marvin and White (110a). Apocynum was administered by mouth in the form of the fluid extract to twelve patients. Although the drug was found to have an action similar to digitalis when given to patients with auricular fibrillation, it produced pronounced gastro-intestinal symptoms, which occurred with the smallest doses that had any demonstrable effect on the heart. Its persistence of action was transient, lasting only twenty-four to forty-eight hours. The drug was much less effective in doses that could be given than digitalis in the treatment of heart disease. Convallaria was also given to twelve patients in the form of the fluid extract. It was found to be distinctly less efficacious than digitalis, causing clinical improvement in only two of

the twelve cases. Nausea and vomiting occurred in nine and diarrhoea in six cases. Its action was transient. Marvin and White conclude that

it would seem from our results that neither apocynum nor convallaria can be substituted for digitalis. In our experience digitalis has been characterized by quicker action, more pronounced effects, less discomfort, and more prolonged improvement, than are seen following either of the other drugs. We are convinced that both these members of the digitalis series have no place in the rational treatment of heart failure.

In spite of the facts that these studies bring out, apocynum and convallaria are used to a considerable extent, as two American pharmaceutical companies reported to Marvin that their annual sales amounted to about 15,000 pints.

In the therapeutic use of digitalis certain requirements should be insisted upon by the medical profession. All products put upon the market should be labelled not only with the results of the biological assay, but also with the date of manufacture and of the assay. The dose should be indicated according to the actual strength of that particular preparation. When the medical profession learns to regulate the dosage of the digitalis bodies properly, and to understand thoroughly the indications for their use, the great value of this group of drugs in the treatment of heart-failure will be more generally appreciated even than it is at present. The selection of the form in which the drug is used is relatively unimportant if activity and especially dosage are properly controlled, and if the use of the unsuitable members of the digitalis group is avoided.

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